THE TREATMENT OF DIPHTHERIA BY ANTITOXIN.

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THE TREATMENT OF DIPHTHERIA BY ANTITOXIN.[1]

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I SHALL endeavor in this paper, after a brief historical introduction, to present some of the more important general considerations bearing upon the treatment of diphtheria by antitoxic serum, together with statistics of results already reported, with the expectation that those who are to follow in this discussion before the Association will be able to offer the results of personal experience in the application of the new remedy.

In July, 1889, Babès and Lepp, in an article entitled "Recherches sur la Vaccination Antirabique,"[2] published results of experiments undertaken to solve the question, "Whether the fluids and cells of animals which have been rendered by vaccination immune have not become vaccines and capable of protecting also other organisms?" The results of these experiments showed that the blood of dogs thoroughly vaccinated against rabies, when injected into susceptible animals, conferred a certain amount of protection against the effects of subsequent inoculation with the rabid virus, and appeared capable of preventing the development of rabies even when the injection of the immune blood was made immediately after the reception of the virus. The authors concluded that "one must admit the possibility of vaccinating with the fluids and cells of animals which have been rendered refractory to the disease."

[1] This paper is based upon the address made by the writer at the opening of the discussion on this subject before the Association. It is considerably expanded beyond the limits of the address, and I have endeavored to bring it up to the date of sending it to the printer (July, 1895).

[2] Babès and Lepp: Annales de l'Institut Pasteur, July, 1889.

Richet and Hericourt are sometimes quoted as the first experimenters to show that the blood of animals is capable of conferring protection upon susceptible animals, but their work has no reference to modern serum-therapy, as their experiments were made with the blood of dogs which had not previously been vaccinated or treated in any way.

The first publication clearly demonstrating the principles of serum-therapy was made by Behring and Kitasato on December 4, 1890, in an article in the *Deutsche medicinische Wochenschrift*, entitled, "Ueber das Zustandekommen der Diphtherie—Immunität und der Tetanus—Immunität bei Thieren." Although in this article the immunizing and curative property of the blood and blood-serum of artificially immunized animals was demonstrated only for tetanus, the application of the same principle to diphtheria was indicated in the same article and in a second paper by Behring in the following number of the same journal.

The first public announcement of the demonstration of the power of the blood-serum of animals artificially immunized against diphtheria to protect and cure susceptible animals inoculated with the diphtheria bacillus or its poison was made by Behring in the report of experiments made by himself and Wernicke, and communicated to the Seventh International Congress of Hygiene and Demography, held in London in August, 1891. There followed in 1892 the article by Behring and Wernicke,[1] in which these experiments were fully described, and which sets forth the fundamental principles underlying serum-therapy of diphtheria.

The first trial of immune serum in the treatment of human diphtheria was made in von Bergmann's clinic, in Berlin, in the autumn of 1891. This trial, together with those made in 1892 by Henoch, in Berlin, by Heubner, in Leipzig, and in the Institute for Infectious Diseases in Berlin, were of a tentative nature and made with weak serum and insufficient doses.

It was not until early in 1893 that Behring succeeded in obtaining antidiphtheric serum equalling the strength of even his so-called normal serum, of which sixty times the strength is that of the weakest Behring serum at present in use. In April, 1893, Behring referred to 30 cases treated with this normal serum. Of these cases, 11 treated in the Institute for Infectious Diseases were reported in detail by Kossel.

From this period on Behring and Ehrlich succeeded in obtaining healing serum of greater and greater strength, until in August, 1893, Ehrlich and Wasserman obtained from goats healing serum twenty to sixty times the strength of Behring's normal serum. At the Eleventh

[1] Behring and Wernicke: "Ueber Immunisirung und Heilung von Versuchthieren bei der Diphtherie." Zeitschrift für Hygiene, Bd. xii.

International Medical Congress, held in Rome (March 29 to April 5, 1894), Heubner reported the results of his experience with the serum-treatment of human diphtheria. His observations, however, were made on cases treated with much weaker antitoxin than is now recognized as suitable.

In April, 1894, Ehrlich, Kossel, and Wasserman reported briefly the results of treatment of 220 cases in six Berlin hospitals, the inception of the treatment in these cases dating from June, 1893, but the great majority of the cases occurring after December, 1893. These cases, with additional ones making a total of 233 cases, with a fatality of 23 per cent., were reported more fully in an article by Kossel in the *Zeitschrift für Hygiene*, in July, 1894. The era of serum-treatment of human diphtheria by approximately sufficient doses of antitoxin really begins with this publication of Ehrlich, Kossel, and Wasserman in April, 1894, although, even in this series of cases, according to later statements of Ehrlich and Kossel, a large number of the cases were treated with quantities of antitoxin which we now consider to be insufficient.

In an address before the Berlin Medical Society, on June 27, 1894, Katz reported the results of antitoxin-treatment dating from March 14, 1894, with Aronson's serum from horses, on 128 cases of diphtheria in Baginsky's service. In the discussion on this address four weeks later, Baginsky completed the series of cases up to 163, with a mortality of 12.9 per cent., and Aronson stated that similarly favorable results had been obtained by Ganghofner in Prague and Escherich in Graz.

In 1893 and the first half of 1894 various articles appeared concerning the preparation of antitoxin, the best methods of estimating its strength, the proper immunizing and therapeutic doses, and similar questions. Since August 1, 1894, Behring's serum prepared at Höchst has been for sale.

It is evident from this brief historical summary that the general principles of serum-therapy of diphtheria were fully established, and its application to human beings in active operation before Roux delivered his memorable address on the subject at the Eighth International Congress of Hygiene and Demography, held in Budapest, September 1–9, 1894, three years after Behring's original communication to the preceding congress in London. Roux, however, presented

the subject with such clearness and force, and with such an array of convincing and carefully analyzed statistical evidence, that the attention of the great body of physicians throughout the world, who had paid little heed to the previous work, was arrested, and the question of the healing power of diphtheria antitoxin became and has continued to be the foremost medical question of the day. From September, 1894, onward the supply of antitoxin from various sources (not all of equally trustworthy character) has become more and more accessible to physicians, and each succeeding month has given birth to a large number of articles on the serum-therapy of diphtheria from various parts of the world.

Unless one denies absolutely the causal relation of the Loeffler bacillus to diphtheria, it must be admitted that the treatment of this disease by antitoxin rests upon a sound experimental basis. The only notable opponent of the view that the Lœffler bacillus is the cause of diphtheria is Hanseman. His arguments, which have been well answered by C. Fraenkel, are equally applicable to the acceptance of the etiological relations of the cholera bacillus, the tubercle bacillus, and many other specific bacteria of infectious diseases. It is not probable that anyone here sides with Hanseman in this matter, so that it is unnecessary to rehearse the arguments which, in my judgment, are conclusive that the Loeffler bacillus is the cause of diphtheria.

The laboratory does not furnish any more impressive experiments than those which demonstrate the power of antitoxic serum to prevent and to cure the disease caused in animals by inoculation with the diphtheria bacillus or its poison. The serum arrests the spread of the local process and abates the symptoms of general toxæmia. These experiments prove beyond question that this healing serum possesses properties which are directly and powerfully antagonistic to the toxic action of the diphtheria bacillus, and there is no good reason to doubt that under similar circumstances this antagonistic power, so readily and surely and uniformly demonstrable in the case of lower animals, will manifest itself also in human beings. The only question, and that, of course, an important one in this connection, is: To what extent the conditions in the treatment of experimental diphtheria by antitoxin are or can be made similar to those in the therapeutic application of the same agent to human diphtheria?

Although it is true that the lower animals are not susceptible, or only

very exceptionally susceptible, to natural infection with the Loeffler bacillus, still there is in my opinion identity in essential points—anatomical, clinical, and etiological—between experimental diphtheria and uncomplicated human diphtheria. The assertion sometimes made that spreading pseudo-membranous inflammations resembling those of diphtheria cannot be produced experimentally in animals by inoculation with the Loeffler bacillus is an error, as I have repeatedly had opportunity to demonstrate by intratracheal inoculations of kittens and rabbits. It is rarely in our power to reproduce experimentally in one species of animal the exact counterpart of a disease caused in another by natural modes of infection, but in the case of diphtheria the resemblance is closer than in most of our attempts to reproduce such diseases by inoculation of their specific germs.

But even if the anatomical and clinical characters of experimental diphtheria are believed by some to differ more widely than I think they do from those of human diphtheria, there remains as the most important point, regarding the matter here under discussion, the conclusive demonstration that in uncomplicated human diphtheria, no less than in experimental diphtheria, the local inflammation at the site of infection is caused by the growth of the Loeffler bacillus, and the lesions of internal parts and the systemic symptoms are due to the absorption of a toxic substance or of substances formed by this bacillus. It would be difficult to understand why an agent with the specific property of neutralizing in the bodies of animals the effects of these toxic substances should be unable to neutralize in human beings similar effects of the same toxic substances, provided this agent can be administered in the proper dose and at the right time.

Dosage and timely administration are factors of prime importance in determining the efficacy of antitoxic treatment. It is our inability to conform to the demands of these factors which has rendered thus far the treatment of tetanus in human beings by antitoxin disappointing. The tetanus antitoxin can be produced by methods similar to those employed in making the diphtheria antitoxin and of a power expressed in immunizing units greater than that of the diphtheria antitoxin. No less striking than in diphtheria are the laboratory experiments in the prevention and cure of artificial tetanus by administration of the tetanus antitoxin, but in this case the dose of antitoxin required to check the disease increases so enormously with increase in

the size of the animal, on the one hand, and with the lapse of time after reception of the virus, on the other hand, that we meet herein most serious obstacles to the successful application of this agent in the treatment of human tetanus.

It has been shown experimentally by Behring, Boer, Roux, and others, that as regards both of these points the conditions are far more favorable for the treatment of diphtheria by its antitoxin than in the case of tetanus. In an animal at a certain time after reception of the tetanus poison the theoretically efficacious dose of the tetanus antitoxin may be a millionfold greater than that required for simple immunization, a quantity too large to administer, whereas the effective dose of the diphtheria antitoxin at relatively the same period may be increased only eight or tenfold. Doubtless the great advantage which we have in the treatment of human diphtheria by antitoxin as contrasted with tetanus is that we are able to recognize and treat the former disease before the production and absorption of a serious quantity of poison.

Only clinical experience can determine what practical difficulties there may be in the way of the successful employment of antitoxic serum in the treatment of human diphtheria; but there is no doubt in my mind that the results derived from experiments on animals justify, nay, demand, the most careful and thorough trial of the new method of treatment upon human beings.

We have no certain knowledge as to the nature of the substances called antitoxins nor as to their mode of action. This is not, however, an argument against their therapeutic employment, for we have no positive knowledge as to the mode of action of many of our therapeutic agents. There are two prominent theories as to the mode of action of the diphtheria antitoxin. The one may be called the chemical, and the other the vital theory. The chemical theory is that the antitoxin directly neutralizes in a chemical sense the toxins. This seemed to be the natural interpretation of the fact that the injection into susceptible animals of a mixture in suitable proportions of the antitoxin and the toxin is harmless, but Buchner and Roux have shown that this earlier view is incorrect, and that by selecting animals of greater susceptibility, or by increasing the natural susceptibility of an animal, the presence of active toxin in the mixture can still be demonstrated. The experimental evidence, therefore, is in favor of the other theory, viz., that the antitoxin acts through the agency of

the living body, and probably in the sense that it renders the cells tolerant of the toxin. The results of the treatment of human diphtheria with antitoxin also speak in favor of this vital theory.

If, as seems probable, the curative effects of the healing serum are brought about through the agency of the living cells of the body, we can understand why these effects will not follow the introduction of the serum with the certainty and precision of a chemical reaction. The cells must be in a condition to respond in the proper way to the introduction of the antitoxic serum. For one reason or another this responsive power may be in abeyance. It may be weakened by intense or prolonged action of the diphtheria poison, or by other previous or coexistent disease or by inherent weakness, or there may even be some individual idiosyncrasy which hinders the customary response of the cells to the antitoxin. Clinical experience shows that cases of diphtheria inherently refractory to timely treatment with antitoxic serum are most exceptional, if indeed they occur at all.

There is some evidence in favor of the view that while antitoxin may exert its protective action upon certain groups of cells, other cells, as for example the nerve-cells, either by their nature or on account of such influences as I have mentioned, may not be equally protected against the toxin. There is also the possibility that the antitoxin may neutralize the effects of certain toxins and not of others present in diphtheria.

Antitoxic serum exerts no bactericidal effect upon the diphtheria bacillus, although when administered in proper quantities sufficiently early in the disease it arrests the spread of the local inflammation which is caused by the bacillus. Virulent bacilli may persist in the throat days and even weeks after recovery following injection of antitoxin.

One of the most important characters of antitoxin is that it requires a definite quantity of this substance to neutralize the effects of a definite quantity of toxin. In animals the curative dose of antitoxin stands in a definite quantitative relation to the size and susceptibility of the individual and to the amount and intensity of the poison in the system. We have no precise method of determining how much and how virulent the poison may be in a given case of human diphtheria, nor how susceptible to the toxin the patient may be. The dosage of antitoxin, therefore, in human diphtheria is empirical, the main factors determining it being

the age of the patient, the assumed duration of the disease up to the time of administering the remedy, and the apparent severity of the disease. As the healing serum is expensive and is capable of inducing unpleasant symptoms, it is desired not to give an excessive quantity. Under these circumstances it may readily happen that an insufficient dose is given and that the administration must be repeated. The general rules regarding the dosage of antitoxin are sufficiently well known not to require mention here, and I speak of this matter only to indicate that because a patient may have received a dose, or even two or more doses of antitoxin, this furnishes no absolute guarantee that a quantity of antitoxin adequate to neutralize the effects of the toxin has been given. We now know that in the early period following introduction of the treatment entirely insufficient doses were given.

Both experiments on animals and clinical experience demonstrate that the earlier antitoxic serum is administered after the inception of the disease the better are the chances of recovery. It is usually impossible to rescue the lives of guinea-pigs by means of antitoxin if the treatment is delayed longer than forty-eight hours after inoculation with an amount of diphtheria poison fatal to these animals in four or five days, although the duration of life may be considerably prolonged. In human beings the conditions are different, but, as will appear from the statistics to be presented, the evidence is conclusive that the superiority of serum treatment over all other methods is most strikingly manifested in the results of the cases in which the antitoxin is given not later than the third day of the disease. Although in many cases the treatment is beneficial when the antitoxin is administered in larger doses at a later period of the disease, the importance of beginning the treatment at the earliest possible date, without waiting to determine by cultures whether or not the Loeffler bacillus is present, cannot be too strongly emphasized.

It is, of course, often impossible to meet this demand for early treatment, as cases of diphtheria are frequently not seen or recognized by the physician, particularly in hospital practice, until after several days' duration of the disease and when grave symptoms have already developed. It is, moreover, in many cases difficult or impossible to determine how long the disease has existed when it is first seen by the physician.

The fact that the benefits of antitoxin treatment become more and

more doubtful the further the disease has progressed and the graver the lesions and symptoms, renders more difficult the collection and analysis of absolutely convincing statistics in favor of the treatment. The accusation is sure to be brought that many of the cases which have responded promptly to early treatment, and these for reasons which have been stated will form a large contingent of the successful cases, were mild cases which would have recovered equally by other methods of treatment. This objection can be fully met only by large series of statistics collected from many epidemics, at different times and in various localities.

The bacteriological study of human diphtheria has disclosed several points important to bear in mind in determining the value of antitoxic treatment. The Loeffler bacillus has been found in healthy throats, although only very exceptionally, unless the person has been exposed to diphtheria. This same bacillus may cause all grades of inflammation of the throat from a mild erythematous angina to the gravest pseudo-membranous inflammations. There has resulted a conflict, not yet settled, between the clinical and the bacteriological diagnosis of diphtheria. As regards these diversities of effect, however, the conditions pertaining to the diphtheria bacillus are in no way different from those relating to many other pathogenic bacteria, as, for example, the pneumococcus, the streptococcus, the cholera bacillus, and even the tubercle bacillus, all of which may be found on healthy mucous membranes and may exert their pathogenic activity with all degrees of intensity. Inconvenient as these facts may be, they must be recognized, and they require a readjustment of previously adopted boundary lines of diagnosis. It would, of course, be absurd to say that a person who harbors in his healthy throat Loeffler bacilli has diphtheria, just as it would be equally ridiculous to consider a person infected with the pneumococcus or the streptococcus when these latter bacteria are present under similar conditions. But it is no less absurd to limit the application of the term "diphtheria" only to those higher degrees of pathogenic action of the Loeffler bacillus characterized by spreading pseudo-membranous inflammations and general toxæmia.

But while the boundaries of the domain of diphtheria have thus been widened by the inclusion of cases not presenting the ordinary clinical characteristics of diphtheria, in another direction they have been restricted by the exclusion of some cases which on clinical

grounds would be diagnosed as diphtheria, but which by bacteriological examination are proved to be caused by other bacteria than the Loeffler bacillus.

The statement is sometimes made that 25 to 30 per cent., or even a larger percentage, of the clinical diphtherias are not genuine diphtherias in the bacteriological sense, but this statement is quite misleading. These figures are based upon the bacteriological examination of large numbers of cases in which there was simply more or less suspicion of diphtheria. They do not relate generally to a large number of cases presenting unmistakable anatomical and clinical characteristics of diphtheria. They are derived from the routine examinations for boards of health and children's hospitals of suspected cases of diphtheria. When one considers that in some cases of diphtheria repeated, painstaking examination, microscopical and cultural, by a skilled bacteriologist is required for the detection of the diphtheria bacillus, it is evident that less reliance is to be placed upon these statistics *en gros* than upon many smaller series reported by bacteriological experts. Of the statistics of the latter character there are many which show that in the series of cases examined (including in each series from a dozen to over three hundred cases), from 90 to 100 per cent. of the clinical diphtherias are due to the Loeffler bacillus. Our experience in Baltimore has been that not over 5 per cent. of the cases which the clinician would confidently diagnose as diphtheria are false diphtheria or diphtheroid. These latter figures relate, of course, to primary diphtheria, and not to the pseudo-membranous anginas complicating scarlet fever and other infectious diseases, a large proportion of which are not referable to the Loeffler bacillus.

I shall consider subsequently in this article the influence which the control of the clinical diagnosis of diphtheria by bacteriological examination is likely to have upon fatality statistics of this disease.

There is an important difference between experimental diphtheria and many cases of human diphtheria, a difference of great significance in determining the scope of efficiency of treatment by antitoxic serum. Our experimental diphtheria is a pure, uncomplicated infection in which only the diphtheria bacillus and its toxins are concerned. On the other hand, in many cases of human diphtheria there are complications and mixed infections due to other micro-organisms, against which, when fully developed, the diphtheria antitoxin is powerless.

The most common and dangerous complicating micro-organism is the streptococcus pyogenes. Bacteriological examinations of fatal cases of diphtheria demonstrate in a large proportion of cases the invasion and pathogenic effects of this most common of all secondary invaders. The confidence with which some observers, particularly of the French school, classify their cases of diphtheria into pure and mixed infections, on the sole basis of the bacteriological examination of the exudate in the throat, does not seem to me justifiable. The complete microscopical and cultural examination of this exudate will, in practically all cases, reveal the presence of other bacteria, and usually of streptococci, besides the Loeffler bacillus. But as these other bacteria are common or regular inhabitants of the healthy throat, their mere presence in this situation is not conclusive evidence that they are engaged in pathogenic action. The abundance of these other bacteria may afford some indication as to their *rôle*, but of greater importance is their demonstration in situations where they are not normally present.

Reiche,[1] in 42 autopsies on cases of diphtheria in which the Loeffler bacillus had been demonstrated during life, made cultures from the kidney and spleen. In 64.3 per cent. of these cases streptococci and staphylococci were found in the kidney or the spleen, and in 45.2 per cent. streptococci were found alone. These cocci must have reached these organs through the circulating blood. He found streptococci in the kidney in one case, which died on the second day of the disease, and positive results were obtained also on the third and fourth day. These results are evidently of much significance in indicating the frequency and the earliness of invasion of complicating micro-organisms in diphtheria and the resulting obstacles to uniformly favorable results of antitoxin treatment.

But the chief evidence in favor of mixed infection must be sought during life in the character of the lesions and symptoms, although these may be misleading. There is also evidence that the failure of a case of diphtheria to respond in the usual way to the timely injection of a sufficient dose of antitoxic serum is an indication of complications and mixed infection.

The opinion is entertained by Roux, Martin, and other French

[1] Reiche: Centralblatt f. innere Medicin, 1895, No. 3.

writers that broncho-pneumonia, one of the most common and serious complications of diphtheria, is due to a large extent to local unhygienic conditions which can be guarded against. Thus they attribute the frequent occurrence of broncho-pneumonia in some groups of their cases to the infection of the hospital wards with the bacteria causing pneumonia, and claim that by improved sanitary conditions this complication may be to a large extent eliminated. Further investigations are needed to determine to what extent this view as to the causation of broncho-pneumonia is justified, but it can scarcely be doubted that this complication is often the result of invasion of the lower air-passages and the lungs by bacteria which are regularly present in the throat, and whose activity is likely to be manifested in this way in many cases of diphtheria, independently of the local sanitary conditions.

Without doubt the remedial *rôle* of diphtheria antitoxin is materially restricted by its inability to combat developed streptococcus sepsis, broncho-pneumonia, and other complications referable to secondary infection, or to stop impending suffocation by immediate removal of mechanical obstacles in the form of false membranes in the air-passages; but the antitoxic serum is the most powerful agent which we possess to prevent the development of these complications and secondary infections. The timely administration of the healing serum, by antagonizing the effects of the Loeffler bacillus, antagonizes in large part the causes of the increased susceptibility to secondary infection, and thus greatly lessens the frequency of their occurrence.

In considering the obstacles in the way of cure of diphtheria by antitoxin the self-evident fact should not be forgotten that this remedy cannot restore cell-life which has already been seriously damaged by the action of the diphtheria bacillus or its poison. The researches of Oertel upon human diphtheria, and those of Flexner and myself upon experimental diphtheria, demonstrate that the toxins of the diphtheria bacillus are most powerful poisoners of cells, the internal lesions of pure diphtheria being especially characterized by widely distributed areas of cell-death. We have no way of gauging accurately at any given period of the disease the extent of the damage already inflicted upon the cells of the body. If the nerve-cells or their axis-cylinders have already been so damaged that paralysis must follow, or the cardiac nerve-cells or muscular fibres have been similarly injured, or the renal

epithelium so affected that degeneration and nephritis ensue, the administration of antitoxin cannot restore those cells which are already on the way to degeneration and death.

This irretrievable damage to cell-life may be present for a considerable time before we are able to recognize its effects. P. Meyer detected pathological changes in the peripheral nerves as early as the third day after the onset of diphtheria and before paralysis was manifest. The occurrence of paralysis, including cardiac paralysis, after antitoxin has been administered even thus early in the disease, cannot, therefore, necessarily be attributed to failure of this agent to neutralize toxin developed after its injection.

Having now considered the experimental basis and the theories of action of antitoxic treatment, the importance of early administration and sufficient dosage, and certain etiological and pathological characters of human diphtheria to be borne in mind in estimating the scope of the treatment, let us turn to the examination of the evidence which has hitherto been published concerning the efficacy of the antitoxic treatment of human diphtheria. This evidence is of two kinds: first, the general impressions of clinicians who have had opportunity to observe the effects of antitoxin administered in a number of cases of diphtheria, and, second, the mortality statistics of cases treated with antitoxin.

Unquestionably great value attaches to the impressions and conclusions of careful clinical observers as to the merits of therapeutic agents. Baginsky has said that naked figures are so little the expression of the endless variations of clinical observation, of all those fortunate and unfortunate accidental circumstances which pertain to the constitution and nutrition of the patient, and of the complications and difficulties which may bring danger in a mild attack or lead to a successful issue an apparently severe attack, that to the clinical observer such figures appear of little value in comparison with the treasure-house of his accumulated experience. And it is to his experience of many years in the same hospital and on similar clinical material that Baginsky repeatedly recurs in his monograph, "Die Serum-therapie der Diphtherie," in support of his favorable conclusions as to the healing power of antitoxin, and this in spite of the fact that his statistical results, leading to the same conclusions, are based upon a larger number of cases than those of any other single observer yet published, and are

among the most convincing of the statistical reports. In explaining why, at the end of ten months' trial of antitoxin, he has determined to commit himself to a definite judgment in its favor, he says:

"The reasons for this are to be found in the continual repetition of improvement and recovery of severe cases which previous experience indicates would have terminated fatally, and, furthermore, in the outcome of an involuntary experiment with interruption of the use of the serum for a period on account of failure in its supply. During this period the mortality of our patients immediately rose again to its former height. The improvement in the general condition of the patients imparts to our diphtheria wards an entirely different character from the former one. That this is not due to any change in the character of the clinical material, to milder forms of the disease, was unfortunately demonstrated by the observations in the months of August and September, when, as by a single blow, we were transported back to the old times, to the same melancholy picture of children deeply prostrated and often in vain struggle with death."

In August and September the supply of antitoxin failed.

The published testimony of those who have had the largest opportunity to study the therapeutic effects of antitoxin is overwhelmingly in its favor. In no less favorable terms than those of Baginsky are expressed the opinions of such observers of high reputation and extended experience as Heubner, von Widerhofer, von Ranke, Ganghofner, Escherich, Bokai, and the Physicians of the Hôpital des Enfants Malades and Hôpital Trousseau, in Paris. These observers have reported already in detail over 2300 cases of diphtheria treated with antitoxin.

Many of those who have reported smaller series of cases, and a few who have reported as many as a hundred cases, have expressed themselves with much caution or have not ventured any final judgment, although in most of these reports the results appeared to be favorable to the new treatment. An example of this conservative position is that of Vierordt, who says that a final decision as to the value of antitoxic serum is not to be expected in the immediate future, as such decision requires a long series of observations in different epidemics and on varied clinical material.

Antitoxic serum is a new and strange remedy, but the effects which follow its injection in individual cases are not new and strange. Nothing happens which the physician may not have occasionally seen to happen in cases treated in the ordinary way. In severe as well as

in mild cases of diphtheria he may have seen an apparently progressive local process quickly arrested and the general symptoms promptly abated. But why should anything new and strange happen after the administration of antitoxin? Cure by antitoxin is cure by Nature's own remedial agent. That which is new and strange is the frequency with which in case after case the timely injection of antitoxin promptly arrests the local inflammation and checks the constitutional disturbance.

Recovery following treatment by antitoxin is such a natural kind of recovery that in any given case the physician may readily have the feeling that the same thing might have happened without the use of the remedy. We can, therefore, understand why it should be those with the largest experience in the treatment of diphtheria by antitoxin who are most decided in expressing their opinion as to its beneficial effects. The very fact that the mode of cure is such a natural one, and unattended by peculiar phenomena, is an obstacle to drawing positive conclusions from a small number of observations, even if these appear most favorable.

That there should be wide diversity in the percentage of cures in reports of different observers is, of course, to be expected when we consider the varied character of the cases treated and the importance of early administration of antitoxin. It may happen that a series of cases is made up so largely of advanced and complicated diphtherias at the time when the antitoxin treatment is begun, that the beneficial effects of the treatment are not apparent. It is, on the whole, remarkable that there should have been so few reports in which the fatality has not been materially diminished during the period of administration of antitoxin.

There are only a very few writers who on the basis of personal experience (in no instance a large one) have expressed an opinion unfavorable to antitoxin. Kohts may be mentioned as one, who on the basis of 47 cases treated with serum, with 29.1 per cent. deaths among the tracheotomized, and 7.6 per cent. among the non-tracheotomized, finds such apparently favorable results no better than by other methods of treatment.

So far, then, as the testimony of physicians based upon their clinical experience is concerned, this, as I have already said, is overwhelmingly in favor of the antitoxic treatment, wherever their experience

in its employment has been a large one. Those with less experience are often even more enthusiastic: but many of these, in view of their limited experience, are wisely conservative and a few are hostile to the new treatment.

But general clinical impressions, convincing as they may be to the individual receiving them, may not be equally convincing to others. They do not furnish any strict scientific proof of the value of a therapeutic agent. If antitoxin really exerts any specific curative action in diphtheria, this must be apparent in the figures of fatality statistics of this disease; and it is only by such statistics, much as they may be decried by some, and difficult as it may be to guard them from errors of interpretation, that a strictly scientific demonstration of the efficacy of antitoxin in the treatment of diphtheria can be brought.

The possible fallacies of interpretation belonging to fatality statistics in general apply in no small measure to those of diphtheria. The case-mortality from diphtheria varies within wide limits according to the more or less severe character of the prevailing epidemic, according to the season of the year, according to the age, according to the method of treatment, in cities and in country districts, etc. Statistics of case-mortality from hospital practice will differ widely from those from private practice, and each of these will differ from the general case-mortality returns from cities. Nor does each of these three classes of statistics represent a uniform material. The material of one hospital may consist very largely of cases of diphtheria admitted in an advanced stage of the disease, or of laryngeal cases sent for operation, while that of another hospital may contain a much larger proportion of cases admitted in early stages of the disease. In general the fatality of diphtheria in hospital practice is higher than that of private practice, as would be expected from the later stage of the disease in which the patients generally enter the hospital; but to this rule there are many exceptions. In some hospitals the patients are all children, in others there may be a considerable proportion of adults with diphtheria. In private practice among the poor, patients may be first seen by the physician frequently in as advanced stages of the disease as in hospitals, and the conditions for successful treatment, and particularly for intubation or tracheotomy, are less favorable for this class of private patients than for hospital patients.

Still other reasons might be given for the lack of uniformity of

diphtheria statistics from different sources; but enough has been said to show that as regards the question which interests us here each report of a series of cases treated with antitoxin requires its own special consideration and analysis, and is not comparable with reports from other sources relating to a different class of cases.

The larger the number of cases embraced in the statistical tables the greater becomes the mutual compensation of such differences as those mentioned, and, therefore, the more trustworthy are the conclusions derived from the statistics; but in collecting the statistics of the general fatality of diphtheria treated with antitoxin it has seemed to me important, for the reasons which have been mentioned, that the tables should contain for each report, as far as possible, statements of the total number of cases treated with antitoxin, of the number and percentage of deaths, of the previous or simultaneous fatality, and of the class of cases, whether in hospital or in private practice. I have also analyzed the cases so far as practicable according to the ages of the patients and according to the day of the disease on which antitoxin treatment was begun. It has seemed to me of especial interest to consider the fatality in operated and not-operated cases. There are, of course, many other points of view which it would have been interesting to consider in the statistical study of the cases reported; but it has seemed to me that the analysis already indicated should suffice to determine the main question at issue, namely, the specific curative power of antitoxin, as well as certain other questions.

It is scarcely ten months since antitoxin has been used by more than a very few favored physicians, and it is a much shorter time since its use has become at all general. In this comparatively short time there have, however, been published more or less definite reports of the results of the treatment in at least 15,000 cases. I have collected 82 reports from 80 different sources, containing 7166 cases. These are presented in Table I. This collection of cases is by no means complete, as I have consulted only the more readily accessible journals; but it is believed to include all of the more important reports. I have not included any reports of single cases, as these are often to illustrate some special point, nor any reports of series of cases less than ten. Indeed, only four reports with less than twelve cases in the group have been included in the tables. Nor have I made use of such merely general published statements without detail, as that there have been treated in

France up to the end of December 2700 cases, with a mortality of 16 per cent.; in Austria, outside of Vienna, 950 cases, with a mortality of 15.7 per cent.; in Croatia and Slavonia, 428 cases, with a mortality of 10.8 per cent.; in Berlin hospitals, 1500 cases, with a reduction in fatality of one-half, etc. Eulenburg has recently (July 15, 1895) made a provisional report concerning the collective investigation inaugurated by the *Deutsche medicinische Wochenschrift*, by sending out cards to be filled out by physicians regarding their results in the treatment of diphtheria with and without serum. Up to the date of the report the cards returned embraced 10,240 cases of diphtheria, of which 5790 were treated with serum and 4450 without serum. The total mortality of the former group was 9.5 per cent.; that of the latter group 14.7 per cent. No further details of this investigation have as yet been published, and these cases are not included in my tables. (See foot-note, page 364.)

I have entirely avoided the duplication of cases, so far as I can determine.[1] There has been no selection whatever of cases. All of the reports of the characters described which came to my notice are included, although many of the early Berlin cases (contained in statistics of Körte, Sonnenburg, and Hahn in my tables) and some of the others were treated with entirely insufficient doses of antitoxin, and some observers have purposely selected, especially at the time when there was little serum to be had, only severe cases for treatment. Kohts' 47 cases could not be inserted, as he does not give the number of deaths in the report which I have seen.

The reports are of unequal value. Some present full and precise details of each case, or of the group of cases, with statements as to previous or simultaneous fatality in the same class of cases in the same locality, whereas others are meagre and unsatisfactory.

Some reports are based upon the bacteriological control of the clinical diagnosis; others upon the clinical diagnosis uncontrolled by bacteriological examination. In general, the statistics from the larger hospitals relate to cases in which the Loeffler bacillus was demonstrated, whereas many of the reports from private practice are without bac-

[1] This duplication of cases appears in several of the published statistics, especially of the Berlin statistics. Thus the cases reported by Schubert, Voswinckel, Canon, and Weibgen appear in the report of Ehrlich, Kossel, and Wasserman, and partly in the reports of Körte, Sonnenburg, and Hahn, sometimes twice repeated. Most of these cases are included without duplication in my table, although they were treated with insufficient doses to a large extent. The cases attributed to Virchow, Aronson, and Katz in some statistics are included in those of Baginsky.

teriological examination. A few, notably Leichtenstern and Wendelstadt, purposely base their observations upon cases in which the diagnosis is purely clinical without bacteriological control.

I shall take this opportunity to consider the influence which the requirement of the bacteriologist, that the clinical diagnosis of diphtheria should be controlled by a bacteriological examination in testing the efficacy of antitoxin treatment, is calculated to have upon the character of statistics intended to show the value of the treatment. It is a favorite criticism of these statistics that the bacteriological, as distinguished from the purely clinical, diagnosis of diphtheria will operate in favor of a low fatality in antitoxin statistics, and that therefore it is unfair to compare these statistics with those which are based upon the uncontrolled clinical diagnosis of diphtheria. Some of the critics would have us believe that the antitoxin statistics, on the one hand, contain a large proportion of cases of mild inflammation of the throat with Loeffler bacilli, but which no clinician would recognize as diphtheria; and, on the other hand, exclude a large proportion of fatal pseudo-membranous inflammations of the throat and air-passages which clinically would be regarded as diphtheria.

In most of the statistical reports from hospitals on antitoxin treatment the statement is expressly made, and it is apparent from the description of the cases, that they do not represent anything else than the usual run of cases of diphtheria as they have regularly for years past presented themselves at the same hospitals. The mild diphtheric sore-throats without clinical evidences of ordinary diphtheria are not likely in any large number to be recognized at all as diphtheria, and still less likely to find their way into general hospitals, from which most of the statistics are derived. Where, as in the statistics of Baginsky and others, sufficient detail concerning each case is reported to enable the reader to form an intelligent estimate of the character and severity of the case, it is evident that affections without the customary anatomical and clinical characters of diphtheria do not enter into the statistics.

It is erroneous to say that the antitoxin statistics are not based upon the clinical diagnosis of diphtheria. The diagnosis is clinical, but with subsequent bacteriological control. The cases are admitted to the hospital with the clinical diagnosis of diphtheria, and the healing serum is or should be at once administered without waiting for the result of the cultures from the throat. Soltmann has been justly

criticised for delaying the injection of antitoxin until after the bacteriological examination was completed.

The assumption that non-membranous anginas and tonsillitis containing Loeffler bacilli figure to any appreciable extent in these statistics is without warrant of facts.

There are treated, of course, together with severe cases, many mild cases with small patches of membrane on the tonsils or in the throat: but such cases are clinically diphtheria or certainly ought to be suspected of diphtheria by the clinician. It is important that such cases, when caused by the Loeffler bacillus, especially in young children, should be treated by antitoxin, for not a few such cases when untreated develop into severe cases, sometimes suddenly into laryngeal diphtheria. Kurth, for example, relates a case in which a twin brother of a child ill with diphtheria was found to present small membranous patches on the tonsils, which during two weeks of observation would at times disappear, and which did not apparently make the child ill. Loeffler bacilli were demonstrated, but the parents would not consent to the injection of serum. At the end of fourteen days laryngeal diphtheria suddenly developed. The injection of antitoxin was followed by recovery in four days. This is simply a type of not a few cases which are regarded as suddenly developed laryngeal diphtheria.

If, as is doubtless true, in some hospitals a larger number of cases are now received for serum treatment in earlier stages of diphtheria than formerly, this is not because the bacteriological diagnosis has supplanted the clinical, but because the importance of early inception of serum treatment has been justly emphasized. The recognition of mild and very mild cases of diphtheria is not a discovery of the bacteriologist, but has long been known to physicians, nor is it a peculiarity of the fatality statistics of cases treated by antitoxin that such mild cases are included in the statistics. They appear equally in previous fatality statistics of diphtheria. Mosler, for example, reports 313 cases of diphtheria with a fatality of 14.5 per cent., treated during a year in the Greifswald clinic before the introduction of serum, and there are numerous other statistics showing that mild cases often preponderate in previous fatality statistics of diphtheria. Nor is the comparison in all of the reports made with former statistics of cases in which the diagnosis is without bacteriological control. In several reports the comparison is with the results of cases in which the Loeffler bacillus was demonstrated, but which were not treated with serum.

As regards the exclusion from antitoxin statistics of cases presenting the clinical characters of diphtheria without the Loeffler bacillus, it is evident, from what has previously been said, that, with thorough bacteriological tests, this can affect only a very small number of cases of unmistakable primary clinical diphtheria. Of the cases concerning which the clinician is in doubt, a considerable proportion are not diphtheria by bacteriological examination, which alone can decide the question. Although some of the non-diphtheric, pseudo-membranous cases are very grave affections, their general mortality is much lower than that of genuine diphtheria. The exclusion from the fatality statistics of diphtheria of the pseudo-membranous cases without Loeffler bacilli is, therefore, the exclusion of a generally milder class of cases, as has been repeatedly demonstrated, and the result is to assign a higher and not a lower fatality to the remaining cases. A few examples taken from reports in Table I. will suffice to demonstrate this. From the statistics of Roux, Martin, and Chaillou 128 pseudo-membranous cases treated with serum were thrown out because they were proven subsequently to be devoid of Loeffler bacilli. The fatality of these cases was only 8.5 per cent., whereas, in the 300 remaining cases which contained Loeffler bacilli and were injected with serum, the fatality was 26 per cent. In Sevestre's and Meslay's statistics 29 cases without Loeffler bacilli, but treated with serum, gave a fatality of 3.4 per cent., as opposed to a fatality of 10 per cent. in the treated cases containing Loeffler bacilli. A similar difference appears in other reports. The serum has no curative influence on pseudo-membranous inflammations not caused by the Loeffler bacillus.

In the best reported statistics information is afforded as to these various points, and the reader can learn the ratio of apparently mild cases and the number and results of the diphtheroid cases.

Although only those statistics which are based upon the thorough bacteriological examination of the cases treated can lay claim to entire accuracy, the benefits of antitoxic treatment are clearly apparent in reports based upon the uncontrolled clinical diagnosis of diphtheria. Of course, in ordinary general practice it is not to be expected that the diagnosis will rest upon a bacteriological examination; but it should be understood that in the absence of such examination there must be occasional instances of apparent failure of antitoxin which would be found explicable had a bacteriological examination been made.

In many reports the percentage of deaths in the cases treated with antitoxin is corrected by excluding cases evidently hopeless on admission, or dying within twenty-four hours after commencement of the treatment. These corrected percentages are usually very materially lower than the rates based on all of the deaths. For example, if the cases dying within twenty-four hours after injection of antitoxin be excluded, the percentage of deaths in Roux, Martin, and Chaillou's cases becomes 21.5 instead of 26; in Baginsky's 13.5 instead of 15.6; in von Widerhofer's 14.3 instead of 23.7; in Vierordt's 14.6 instead of 25; in Lebreton's and Magdelaine's 10.8 instead of 12; in Moizard's and Perregaux's 11.3 instead of 14.7; in Sevestre's and Meslay's 6.6 instead of 10; in Bokai's 18.3 instead of 25.5, etc. I have, however, not used these reduced percentages, although in many instances it might with propriety have been done. The statistics in my tables, therefore, do not give, in many instances, as favorable percentages for antitoxin as may justly be claimed; but, on the other hand, they are more properly comparable with the previous or simultaneous fatality rates from diphtheria, these being based upon the total number of deaths in all of the cases treated. I have aimed to avoid the accusation of selection of cases or of unfair manipulation of the figures.

In the majority of the reports the cases treated are all, or nearly all, of the cases of diphtheria which were admitted to the hospital or came under observation during the period of treatment; but in some it is expressly stated that, in consequence of the cost and the scarcity of the healing serum, mild cases and evidently hopeless cases did not receive the serum. There is no evidence of selection of mild cases in order to obtain results favorable to antitoxin.

The percentages in the column headed "Previous Fatality" are those given by the writers for diphtheria not treated with antitoxin. In some instances they relate to the average fatality for a series of preceding years, in some to the minimum and the maximum fatality for several years, in some to the simultaneous fatality or the fatality during a period of interruption in the supply of serum. In all instances they are the case mortality-rate of diphtheria in the hospital or locality from which the cases treated with antitoxin are derived. The arrangement of the reports is only in part chronological. Following the references to the articles it is stated, so far as could be ascertained, whether the cases were in hospital or in private practice.

TABLE I.—FATALITY OF CASES OF DIPHTHERIA TREATED WITH ANTITOXIN.

Number of cases of diphtheria treated with antitoxin, the number and percentage of deaths, and the previous fatality in 82 reports.

Reporter.	Cases.	Deaths.	Previous fatality.	References.
1. Roux, Martin, and Chaillou.	300	78 (26 per ct.)	50 per ct.	Ann. de l'Institut Pasteur, Sept. 1894 (in Hôpital des Enfants Malades).
2. Kossel,	117	13 (11.1 per ct.)	52–61 "	Deutsche med. Wochen., 1894, p. 946 (hospital).
3. Körte,	121	40 (33.1 per ct.)	45.1 "	Berliner klin. Wochen., 1894, p. 1039 (hospital).
4. Sonnenberg,	95	16 (16.8 per ct.)	27.6 " (period of interruption of serum treatment.)	Deutsche med. Wochen., 1894, p. 930 (hospital).
5. Hahn,	205	49 (24 p. ct.)	41 per ct.	Ibid ,1895, Vereins-Beilage.p.2 (hosp.)
6. Baginsky,	525	83 (15.6 per ct.)	41 "	Die Serumtherapie der Diphtherie, von Dr. Adolf Baginsky. Berlin, 1895 (hospital).
7. Heubner,	207	27 (13 per ct.)	48–52 "	Reported at 13ter Congress für innere Medicin, München, April 2, 1895. Münchener med. Wochen., April 9, 1895 (hospital).
8. von Widerhofer,	300	71 (23.7 p.ct)	50 "	Ibid. (hospital).
9. von Ranke,	96	19 (19.7 p.ct.)	42.2–56 "	Ibid. (hospital).
10. Stintzing,	59	12 (20.1 p.ct.)	25 "	Ibid. (hospital).
11. Rauchfuss,	100	34 (34 p.ct.)	55 "	Ibid. (hospital).
12. von Mering,	74	4 (5 p ct.)	30 "	Ibid. (hospital).
13. von Noorden.	81	19 (23 p.ct.)	45 "	Ibid. (hospital).
14. Schröder,	65	8 (12.7 p.ct.)	30–37 "	Ibid. (hospital).
15. Vierordt,	63	16 (25 per ct.)	41–67 "	Deutsche med. Wochen., 1895, p. 169 (hospital).
16. Rumpf,	22	2 (8 per ct.)	13–28 "	Münchener med. Wochen., Nov. 20, 1894 (hospital).
17. Lebreton and Magdelaine,	258	31 (12 per ct.)	50 "	Le Bulletin Médical, 1895, No. 10 (Hôpital des Enfants Malades).
18. Le Gendre,	17	3 (17.6 per ct.)	50–60 "	Bull. et Mémoires de la Soc. Méd. des Hôpitaux de Paris, Dec. 20, 1894 (Hôpital Trousseau).
19. Moizard and Perregaux,	231	34 (14.7 per ct.)	50–60 "	Journ. de Méd. et de Chirurg., Dec. 25, 1894 (Hôpital Trousseau).
20. Sevestre and Meslay,	150	15 (10 per ct.)	50–60 "	Le Bulletin Médical, 1895, No. 18 (Hôpital Trousseau).
21. Ganghofner,	110	14 (12.7 per ct.)	43.6–78.2 "	Prager med. Wochen., 1895, Nos. 1, 2, and 3 (hospital).
22. Soltman,	89	13 (14.6 per ct.)	27.2 "	Deutsche med. Wochen., 1895. No. 4 (hospital).
23. Bokai,	176	42 (24 per ct.)	53.5–67.5 "	Ibid., 1895, No. 15, and Wiener med. Presse, 1895, No. 12 (hospital).
24. Escherich.	51	5 (9.5 per ct.)	.....	Abstract in Münchener med. Wochenschrift, 1895, No. 7 (hospital).
25. Gnändinger,	27	11 (40.7 per ct.)	36–45 5 p.ct.	Wiener klin. Wochenschrift, 1895, No. 1 (hospital.)
26. Monti,	25	1 (4 per ct.)	.....	Wiener med. Wochen., 1895, Nos. 4 and 5 (hospital).
27. Heim,	27	6 (22 per ct.)	52.5 per ct.	Ibid., 1895, No 4 (hospital).
28. Unterholzner,	31	8 (25.8 per ct.)	66.7 "	Ibid. (hospital).
29. Bäumler,	26	2 (7.7 per ct.)	.....	Münchener med. Wochen., 1894, p. 1062 (hospital).
30. Börger,	30	2 (6.66 per ct.)	20 per ct.	Deutsche med. Wochen., 1894, No. 48 (hospital).
31. Hilbert,	11	0	.....	Ibid., 1894, Vereins-Beilage, p. 142 (hospital).
32. Hager,	25	1 (4 per ct.)	.....	Centralbl. f. innere Medicin, 1894, No. 48 (private practice).
33. Moeller,	76	27 (35.5 p.ct.)	.....	Ibid. (hospital).
34 Kuntzen,	25	3 (12 per ct.)	.....	Deutsche med. Wochen., 1894, No. 49 (hospital).
35. Schmidt,	14	3 (21.4 p.ct.)	....	Ibid., 1894, No. 52 (private practice).
36. Seiz,	27	1 (3.6 per ct.)	30.6 per ct.	Therapeut. Monatshefte, Dec. 1894 (private practice).
37. Charon,	13	4 (30.8 per ct.)	.....	Annales de la Soc. Royale des Sci. Médicales et Naturelles de Bruxelles, 1894, t. iii. p. 337 (hospital).
38. Washbourn, Goodall, & Card,	72	14 (19.4 per ct.)	36–41.8 p. ct.	British Med. Journ., Dec. 22, 1894 (hospital).
39. Seitz,	35	2 (5.7 per ct.)	.....	Abst. in Münchener men. Wochen., 1895, No. 12 (hospital?).

Reporter.	Cases.	Deaths.	Previous fatality.	References.
40. Pavlik,	13	1 (7.7 per ct.)	.....	Wiener med. Presse, 1895, Nos. 1 and 5 (private practice).
41. Handler,	32	5 (15.6 p. ct.)	.....	Ibid., No. 6 (private practice).
42. Herringham,	18	3 (16.7 per ct.)	.....	British Med. Journ., Dec. 22, 1894 (hospital).
43. Caiger,	30	8 (26.6 p.ct.)	30 per ct.	Ibid., Dec. 29, 1894 (hospital).
44. Hall,	11	3 (27.3 p.ct.)	31.25 per ct.	Ibid., Jan 19, 1895 (hospital).
45. Tirard and Willcocks,	10	1 (10 p. ct.)	38 per ct.	The Lancet, Jan. 19, 1895 (hospital).
46. Ruffer,	274	37 (13.5 per ct.)	.....	Cases treated in four London hospitals, Brit. Med. Journ., Feb. 2, 1895.
Epidemic in Trieste:				
47. Private practice,	72	5 (6.5 per ct.)	43.8–62.6p.c.	Das Oesterreichische Sanitätswesen, Jan. 3, 1895.
48. Hospital.	180	40 (22.2 p. ct.)		
49. Blumenfeld,	50	2 (4 per ct.)	.....	Wiener klin. Wochen., 1895, No. 3 (private practice).
50. Witthauer,	36	5 (14 per ct.)	.....	Therapeut. Monatshefte, Feb. 1895.
51. Dreyfus,	78	15 (19.3 p. ct.)	50 per ct.	Lyon Médical, Feb. 3, 1895 (hospital).
52. Simon,	16	2 (12.5 per ct.)	.....	La Médecine Moderne, Feb. 6, 1895 (private practice).
53. Malvoz,	15	1 (7 per ct.)	.....	Le Scalpel, Feb. 17, 1895
54. Gougenheim,	125	12 (9.5 per ct.)	21.1 per ct.	Ann. des mal. de l'Oreille, du Larynx et du Pharynx, 1895, No. 5; abst. in the Med. News, June 15, 1895 (hosp.)
55. Rapmund,	100	7 (7 per ct.)	20–30 per ct.	Zeitschrift f. Medizinal-Beamte, Feb. 15, 1895 (collective investigation of use of antitoxin in private practice in district of Minden).
56. Schüller,	32	1 (3.1 per ct.)	.....	Allgem. med. Central-Zeitung, 1895, No. 88 (private practice).
57. Grünfeld,	12	1 (8.3 per ct.)	.....	Abst. Schmidt's Jahrb., 1895, Bd. 246, p. 37 (private practice).
58. Schaewen,	15	0	.....	Berliner klin. Wochenschrift, 1895, No. 10 (private practice).
59. Heidenhain,	24	3 (12.5 per ct.)	.....	Ibid. (private practice).
60. Risel.	114	9 (7.9 per ct.)	.....	Deutsche med. Wochenschrift, 1895, No. 10 (hosp. and private practice).
61. Weiland,	20	0	.....	Ibid. (from private practice of six physicians in Baden).
62. v. Muralt,	58	2 (3.4 per ct.)	.....	Correspondenzbl. f. Schweizer-Aerzte, 1895, No. 5 (hospital).
63. Blattner,	38	9 (23.6 per ct.)	.....	Abst. in Münchener med. Wochen., March 5, 1895 (hospital).
64. Gerloczy,	55	15 (27.3 p. ct.)	.....	Abst. ibid. (hospital).
65. D'Espine,	60	6 (10 per ct.)	.....	Rev. méd. de la Suisse Romande, (April 20, 1895 (40 cases in hospital).
66. Mya,	17	2 (11.8 per ct.)	.....	Wiener med. Blätter, 1895, p. 760 (hospital).
67. von Engel,	39	10 (25.5 p.ct.)	50 per ct.	Prager med. Wochenschrift, 1895.
68. Fischer,	225	35 (15.5 per ct.)	.....	New York Med. Record, April 6, 1895 (hospital, consultation and private practice).
Biggs:				
69. Treated in city by sanit'y inspectors,	255	40 (15.69 per ct.)	25–35 per ct	Ibid. April 20, 1895.
70. Treated at Willard Parker Hosp.	164	45 (27.4 per ct.)	32 per ct.	
71. Lennox Browne,	45	2 (4.4 per ct.)	34 per ct.	Le Bull. Méd., 1895, No. 21 (hospital).
72. Codd and Whitehouse,	11	4 (36.4 per ct.)	.....	Brit. Med. Journ., May 18, 1895 (hosp.).
73. Winkfield,	22	4 (18.2 p. ct.)	36 per ct	Ibid., May 11, 1895 (hospital).
74. Horowitz,	21	1 (4.8 p. ct.)	10.7 per ct.	Abst. in Münchener med. Wochen., May 7, 1895 (hospital).
75. Sigel,	100	12 (12 p. ct.)	40–50 per ct.	Abst. ibid., May 21, 1895 (hospital).
76. Howard,	40	3 (7.5 p. ct.)	.....	The Medical News, June 1, 1895 (private practice).
77. Van Nes,	52	12 (23 per ct.)	36–48 per ct.	Deutsche med. Wochen., June 6, 1895 (hospital).
78. Leichtenstern & Wendelstadt,	123	25 (20.3 per ct.)	30.9 per ct.	Münchener med. Wochen., June 11, 1895 (hospital).
79. Kurth,	97	10 (10.3 per ct.)	.....	Deutsche med. Wochen., July 11, 1895 (35 hospital cases).
80. Timmer,	31	6 (19.4 per ct.)	.....	Abst. in Deutsche Medizinal-Zeitung, June 10, 1895 (hospital).
81. Cases treated in Cartagena,	156	21 (13.5 per ct.)	.....	Abst. in Brit. Med. Journ., July 6, 1895.
82. Mason,	306	81 (26.4 per ct.)	45–52 per ct.	Reported to Assoc Amer. Phys., May 31, 1895. Abst. in Med. News, June 15, 1895 (hospital).
Total, 82 reports,	7166	1239 (17.3 per ct.)		

The fatality of 7166 cases of diphtheria treated with antitoxin was 17.3 per cent.

The previous or simultaneous fatality of cases not treated with antitoxin is stated in 45 reports. These reports contain 5406 cases treated with antitoxin, with 1008 deaths, a fatality of 18.6 per cent. Estimating the number of deaths in these cases upon the basis of the previous or simultaneous fatality for each group (taking the lowest figures given), there would have been 2279 deaths, or 42.1 per cent. There was, therefore, an apparent reduction of case-mortality by the use of antitoxin of 55.8 per cent.[1]

It appears from Table I. that of 7166 patients with diphtheria treated with antitoxin 1239, or 17.3 per cent., died. Among these cases are included many treated during the early period after the first introduction of the treatment with entirely insufficient doses. There are also included a large number of cases dying from complicating diseases not referable to diphtheria, or dying within twenty-four hours after beginning the treatment, cases which cannot properly be regarded as indicating failure of the serum treatment. The great bulk of the statistics come from children's hospitals. Under these circumstances, indeed, from any point of view, the fatality derived from Table I. of cases treated with antitoxin is very low. There is, however, no standard of comparison for the fatality in this entire group of cases. It cannot be compared with fatality statistics from hospitals nor with those from private practice. The table contains at least five to six times as many cases from hospital practice as from private practice. The ratio of deaths to all cases, therefore, is greater than could be expected from the returns of all cases similarly treated in cities; but even in comparison with municipal fatality statistics of diphtheria during the prevalence of mild types of the disease the percentage of deaths is very low. This strikingly low fatality in itself speaks strongly in favor of the efficiency of the serum treatment.

[1] The report of Fürth concerning the results of serum treatment in the medical and surgical clinics at Freiburg was published too late to be included in my tables; 100 cases were treated, with a fatality of 12 per cent. During the five preceding years the fatality from ordinary treatment fluctuated between 31 and 49 per cent., averaging 39 per cent. The same average existed during the seven months of the year corresponding to the period during which the antitoxin was used. There was laryngeal involvement in 43 cases, and tracheotomy was performed in 31, with 11 deaths (35.4 per cent.). In previous years tracheotomy had been required in 46.2 per cent. of the cases, with a mortality of 70.4 per cent. (Abstract in *The Medical News*, August 17, 1895.)

In 46 reports contained in the table the previous or simultaneous percentage of deaths from diphtheria not treated with antitoxin is given for the same hospital or locality in which were the cases treated with antitoxin. These reports contain 5406 cases of diphtheria treated with antitoxin with 1008 deaths, or 18.6 per cent. If we calculate the number of deaths in each series of these cases upon the basis of the previous fatality, selecting the lowest percentages given, we have 2279 deaths, or 42.1 per cent. There is, therefore, on this estimate, by the use of antitoxin, an apparent reduction in the number of deaths of 55.8 per cent. There must be a much greater difference between the characters of the cases composing the two groups compared than appears from the statements of the writers and the details of the cases described, if this striking reduction in fatality is not due in large part to the serum treatment.

If we separate the hospital cases from those in private practice, we obtain from 61 reports of Table I. 5777 cases of diphtheria treated with antitoxin in hospitals. These furnished 1081 deaths, giving a percentage of 18.7. Although this is not an unheard-of fatality of diphtheria in hospitals, it is most exceptional, and I am not aware that an equally low fatality has been observed in hospitals receiving large numbers of cases of diphtheria in children. The fourth column in Table I. gives the percentages observed in many such hospitals.

There are 41 reports which give for the same hospital the previous percentage of deaths from diphtheria not treated with antitoxin. These furnish 4899 cases treated with antitoxin, with 944 deaths, or 19.3 per cent. If we calculate the number of deaths which would have occurred among these cases had the percentage of previous fatality obtained, selecting the lowest percentages given, there would have been 2130 deaths, or 43.5 per cent. The apparent diminution in the number of deaths as the result of serum treatment is, according to this estimate, 55.6 per cent. If we had selected only the larger and most carefully analyzed and satisfactory statistics from the principal hospitals—in large part children's hospitals—there would have been in over 3000 cases an apparent reduction in fatality of 60 per cent.

There may occur considerable differences in the annual fatality from diphtheria in a hospital during a series of years; but such differences between the minimum and the maximum fatality as that just noted between the actual and the estimated fatality are most exceptional.

In the Friedrichshain hospital in Berlin there has been observed a difference of 28 per cent. in the annual fatality from diphtheria. The largest difference observed in the surgical clinic in Berlin during ten years was that between 43.2 per cent. in 1888 and 58.5 in 1890.[1] In the report of the Metropolitan Asylums Board[2] in London, where the case-mortality from diphtheria in hospitals is generally much lower than on the continent, the fatality in 1889 was 40.7 per cent.; in 1890, 33.5 per cent.; in 1891, 30.6 per cent.; in 1892, 29.3 per cent.; in 1893, 30.4 per cent. This apparent reduction in fatality since 1889 in large part disappears if only patients under fifteen years of age are considered, the corresponding percentages for these being respectively 40.7, 41.6, 36.9, 35.6, and 37.

The natural interpretation of our statistics, showing in over 7000 cases, of which at least five-sixths are from hospital practice, treated with antitoxin an extraordinary low percentage of deaths for this class of cases, and showing an apparent reduction in fatality of from 50 to 60 per cent. by the use of antitoxin, is that the antitoxin exerts a specific curative power over diphtheria.

What are the objections which may be and have been urged against this natural interpretation of the statistical evidence?

In the first place, it has been claimed that these observations have been made during the prevalence of unusually mild diphtheria. In some places the prevailing type of the disease seems to have been mild; but the great majority of the observers quoted in the table consider that the prevailing diphtheria in their localities has been of average severity, and they cite in many instances the simultaneous fatality of cases not treated with antitoxin as proof that the disease is not of peculiarly mild type; indeed, in several places it seems to have been of more than average severity. During the period in which Roux treated with antitoxin 300 cases in the Hôpital des Enfants Malades, with a fatality of 26 per cent., the fatality in the Hôpital Trousseau, also in Paris, and receiving a similar class of cases, was 60 per cent.

But even if it be admitted, for the sake of argument, that the prevailing type of diphtheria during the past year has been mild, it is to be considered that the influence of this milder type upon the cases

[1] V. Hirsch: Archiv. f. klin. Chirurgie, Bd. 49, Heft, 4.
[2] British Medical Journal, December 25, 1894.

received in many hospitals appears chiefly in the reduction of their number, and far less in a change in the character of the cases admitted. This is the statement of von Ranke, of Bokai, and of several other physicians in charge of diphtheria-wards. They say that so far as their hospitals are concerned, as a rule, severe and advanced cases are sent there by physicians in the city, often for operation to relieve laryngeal stenosis, and that when the epidemic is mild in character they receive fewer cases, but not many milder cases. Doubtless these conditions will not hold for all hospitals, particularly not for such as are intended for the compulsory isolation of all cases of diphtheria which cannot be properly isolated at their homes, but they are probably applicable in large part to most of the hospitals from which come the reports now under consideration.

So far as I can judge, no proof has been brought forward in support of the opinion that the low percentage of fatality of diphtheria treated with antitoxin can be referred in any large measure to the prevalence of an unusually mild type of the disease, although in a few scattered groups of cases, particularly some of the smaller series in my table, this may be in part the explanation.

I attach decidedly more weight to a second criticism of antitoxin statistics which has been made, namely, that in hospitals where the serum treatment has been carried out a proportionately larger number of cases are received now than formerly in the earlier stages of diphtheria. The advocates of the treatment have properly insisted upon the importance of early injection of the serum, and, especially during the time when the serum was not to any extent in the hands of general practitioners, and it would be natural to suppose that physicians would send their patients and parents take their children to such hospitals as soon as possible after recognition of the disease. Inasmuch as with any approved method of treatment of diphtheria the results are better the earlier it is begun, it is evident that statistics based on the former experience with the treatment of diphtheria in hospitals would not be altogether comparable with the antitoxin statistics from the same hospitals.

It is, however, very difficult to say how much allowance is to be made for this criticism. There has been widespread skepticism among physicians and the general public as to the value of the treatment. Thus Rapmund, in his efforts to establish in the district of Minden a

collective investigation of serum-therapy in diphtheria, found the physicians so skeptical that of 194 practitioners only twenty would use it at all, and only two employed it extensively. There are also statements as to the unwillingness of parents to have it tried on their children. Many of the reports state that during the period of serum treatment cases were not received in any earlier stages of the disease than formerly; in a few of the reports, as, for example, in that of Kuntzen from Oschersleben, it is said that physicians were induced to send their patients early in the disease. In Berlin and some other cities there has been a marked increase in the number of patients with diphtheria admitted to hospitals since the introduction of the serum treatment, and this has been without a corresponding increase in the total number of cases in the cities. Heubner in his recent address at the Congress of Internal Medicine, at Munich, admits that lighter cases of diphtheria go to the hospital now, but that this is not enough to explain the great difference in fatality. There are undoubtedly considerable differences in different hospitals as to the proportion of cases admitted in early stages of diphtheria, but in many of the hospitals where the benefits of antitoxin have been most apparent, as contrasted with the previous results, it is expressly stated that the number of mild cases admitted is no greater than formerly.

If we make all due allowance for this increase in the proportion of early cases treated in hospitals, and certainly some allowance must be made, this factor is still altogether inadequate to explain the great reduction in fatality of diphtheria treated with antitoxin. This will also be apparent later when we consider the results of treatment according to the day of the disease on which it is begun.

A third criticism, namely, that the bacteriological control of the diagnosis of diphtheria operates in favor of a low mortality in antitoxin statistics has already been fully discussed.

It is manifestly improper to compare the average mortality of thousands of cases treated in hospitals with antitoxin with exceptionally favorable results at certain periods in a few hospitals in a comparatively small number of cases without serum treatment, and still more improper, as has even been done, to make such comparison with the most favorable percentages which one can find reported from private practice or in municipal mortality statistics. Surely some consideration must be given to the previous and simultaneous results obtained from

cases without serum treatment in the same hospitals from which the cases reported are derived.

We have now considered the principal objections which have been made to the natural interpretation of statistics, showing an apparently great reduction in the fatality of diphtheria by the use of antitoxin. I believe that it has been shown that, even if all possible allowance be made for such assumptions as those considered, they are still wholly inadequate to account for an apparent reduction in the deaths from diphtheria by antitoxin treatment of 50 to 60 per cent. in nearly 5000 cases collected from hospitals in Germany, France, Austria, England, and America, and reported by forty different physicians, most of whom are of high reputation and large experience. These statistics seem to me to establish beyond all reasonable doubt the conclusion that antitoxin is a specific curative agent for diphtheria.

It has been contended that the only absolutely convincing proof of the curative efficacy of antitoxin is the demonstration of a marked reduction in the total number of deaths from diphtheria in a city or town in proportion to all of the cases. Municipal mortality and morbidity statistics are necessarily far less accurate than hospital statistics, and, for reasons which have been stated, the prevalence of a mild type of diphtheria will have greater influence upon municipal mortality statistics for diphtheria than upon hospital statistics. It is to be expected that when sufficient time has elapsed and the employment of antitoxin in the treatment of diphtheria has become sufficiently general, the reduction in mortality by its use will be apparent in general mortality statistics. At present we have little information upon this point. The mere statement of the total number of deaths without knowledge of the morbidity and of the prevailing type of disease is, of course, not decisive for either side of the question; but so far as it goes it is interesting to learn that in Boston, during the antitoxin period (January 1 to May 1, 1895) the total fatality from diphtheria was 14 per cent., as compared with a fatality of 31 per cent. during the corresponding period of previous years (Mason), and that in Carthagenia, Spain, during four months of employment of antitoxin, the total number of deaths was only one-fourth the average number for the same period of time during the preceding ten years.

The only antitoxin statistics which I can find based upon such

material as composes municipal fatality statistics are those of Risel and of Kurth.

Risel reports the results in all of the cases treated by antitoxin during two months in the city of Halle. They are derived from the practice of thirty physicians among the poor and the rich, in the houses of the patients and in hospitals, and include mild and severe cases as they presented themselves. Of the 89 patients treated in their homes, almost without exception children not over seven years of age, 6 died, giving a fatality of 6.7 per cent.; 19 of these had laryngeal diphtheria, of whom 4 died. Of the 25 patients treated in hospitals, 3 died, a fatality of 12 per cent.; 15 of these had laryngeal involvement, of whom 3 died. The total fatality was 7.9 per cent. No data are given for comparison with the previous or simultaneous fatality of cases not treated with serum. In only a few cases, and these in hospitals, was the clinical diagnosis confirmed by bacteriological examination.

Kurth reports the results of serum treatment in the practice of sixty physicians in Bremen, and a few outlying villages, from October 8, 1894, to January 31, 1895. A circular-letter was sent from the Bacteriological Institute to every physician in the city, and apparently general co-operation on the part of the physicians and the public officials was secured. In 97 cases treated with serum the diagnosis of diphtheria was established, in the great majority of the cases by demonstration of the Loeffler bacillus controlling the previous clinical diagnosis. The total case-mortality was 10.3 per cent. The fatality of the 64 cases treated in the city (hospital and private practice) was 7.8 per cent.; that of 33 cases derived from the surrounding country district was 15.2 per cent.; that of 35 cases treated in the city hospitals was 14.3 per cent. Laryngeal diphtheria occurred in 66 per cent. of the cases in country districts and in only 36 per cent. of the cases in the city. This and the generally less favorable results in country practice are attributed by Kurth, not to greater severity of the epidemic in the former, but to the custom in the country of not calling a physician until the symptoms are urgent, and to the greater distance which physicians have to travel. If the bacteriological control of the diagnosis be disregarded—that is, if all the cases diagnosed clinically as diphtheria and treated with serum be considered—the fatality was 9.4 per cent.; another illustration that bacteriological

control of the clinical diagnosis results in higher, not as some have claimed in lower, percentage of deaths. Of the 50 cases of clinical diphtheria, all of the cases being included which did not show Loeffler bacilli, the fatality was only 6 per cent. During the serum period there occurred 25 cases of diphtheria not treated with antitoxin, with a fatality of 24 per cent. During the same period of the year in which the serum-treated cases occurred there were during the preceding year 148 cases of diphtheria, with a fatality of 32 per cent.

It must be conceded that these interesting reports of Risel and of Kurth speak strongly in favor of the possibility of bringing about a great reduction in the general fatality from diphtheria in cities by treatment with antitoxin. As a larger proportion of the cases in private practice can be treated in early stages of the disease than in hospitals, this reduction should be greater than that already shown by hospital statistics.

A most convincing demonstration of the healing power of antitoxin is furnished by the experience of Baginsky during an involuntary pause in the serum treatment caused by failure in the supply of serum. Between March 15, 1894, and March 15, 1895, there were treated in Baginsky's service by antitoxin 525 children, with a fatality of 15.6 per cent. During the period of forced interruption of the serum treatment, this period being chiefly the months of August and September, 126 children were treated without antitoxin, with a fatality of 48.4 per cent. There was absolutely no selection of cases in either group. In his comments upon this experience Baginsky says:

"It is all the more remarkable as the ratio of mortality of those treated with the serum, both before and after the period of interruption, varied within very small percentage figures. If one will permit figures to speak at all, there has scarcely been made on human beings a more demonstrative test of the curative power of a therapeutic agent. It was an experiment forced upon us, but it proved to us how terrible was the form of disease which we were treating, and how numerous would have been the victims without the use of the healing serum."

A similar experience has been reported by several other writers. Thus Körte noted a rise in fatality from 33.1 per cent. during the serum period to 53.8 during the period of failure in the supply of serum; Ganghofner, under similar conditions, a rise from 12.7 per cent. to 53.2 per cent.: Heim, from 22 per cent. to 65.6 per cent., and

during the epidemic in Trieste the fatality rose from 18.7 per cent. to 50 per cent., when the serum failed. All of these highly significant observations were made on cases occurring in the same epidemic, the period of enforced interruption of the serum treatment being preceded and followed by the periods of serum treatment.

We have considered thus far mainly the hospital statistics. These are, for manifest reasons, more numerous, larger, and more carefully analyzed than those from private practice. It is, however, in private practice, especially among those classes who are in the habit of calling a physician early in the disease, that the best results from serum treatment are to be expected, for here there is more frequent opportunity for timely treatment. A glance at Table I. will show that in general the fatality of diphtheria treated with serum in private practice is much lower than in hospitals.

If we summarize the 18 reports from private practice in Table I., we have 663 cases of this class treated with antitoxin and among these are 46 deaths, giving a fatality percentage of only 6.9. This would indicate that the serum treatment may reduce the fatality from diphtheria in private practice to nearly one-third that under the same treatment in hospitals. Some of the reports of the results of serum treatment in private practice furnish, indeed, most remarkable evidence of the efficacy of this treatment.

Most of the reports attempt some sort of classification of the cases treated with antitoxin. The simplest and most common, although not the most valuable, is the division according to degrees of apparent severity, expressed by such epithets as mild, moderate, severe, very severe. Such a classification is, of course, only of limited value, as even the mildest case of diphtheria may unexpectedly assume a malignant character. If, as we believe to be proved, antitoxin injected in time arrests the local process and the constitutional disturbance, then many of the cases which appear under the head of mild cases in antitoxin statistics would, under other methods of treatment, have become severe cases, and would be so recorded. Indeed, with the early administration of antitoxin there should be comparatively few severe cases.

The classification of diphtheria adopted by Roux into angina and croup with and without microbic association has been followed by

some of his successors. So far as this classification is actually based upon a correct separation of pure diphtheria from diphtheria with mixed infection, it is of the utmost importance in determining the relative value of antitoxin in the treatment of these two divisions of diphtheria. I have already expressed the opinion, however, that the bacteriological examination of the exudate and secretions in the throat is not decisive in determining the presence or absence of mixed infection. Still Roux's analysis of his cases on this basis indicated clearly that the serum was far more efficacious in diphtheric anginas and croup which yielded pure cultures of the Loeffler bacillus than in those which gave in addition to the Loeffler bacillus cultures of other pathogenic bacteria. In presenting these results the epithet "pure" applied to angina or croup is to be understood to signify that only the Loeffler bacillus was found in the cultures, and the epithet "associated" to signify that this bacillus was found in cultural association with the coccus of Brisou, staphylococci or streptococci, most commonly the last. The "corrected" percentages are those obtained after subtracting deaths occurring within twenty-four hours after admission.

Of the 300 cases treated with serum with a total fatality of 26 per cent. reported by Roux, Martin, and Chaillou, there were 120 pure anginas, fatality 7.5 per cent. (corrected 1.7 per cent); 49 associated anginas, fatality 24.2 per cent. (corrected 17.7 per cent.); of not operated croup, 4 pure, fatality 0; 6 associated, fatality 16.6 per cent.; of operated croup, 49 pure, fatality 30.9 per cent. (corrected 24.4 per cent.), and 72 associated, fatality 56.9 per cent. (corrected 43.1 per cent.).

Of Moizard and Perregaux's 231 cases, total fatality 14.7 per cent., there were 44 pure anginas, fatality 4.5 per cent.; 42 associated anginas, fatality 14.3 per cent.; 94 pure croup, fatality 18.5 per cent.; 51 associated croup, fatality 17.6 per cent. No correction is made in these percentages.

Of Sevestre and Meslay's 150 cases, total fatality 10 per cent., there were 29 pure anginas, fatality 3.4 per cent.; 24 associated anginas, fatality 12.5 per cent. (corrected 8.3 per cent.); 67 pure croup, fatality 8.9 per cent. (corrected 7.5 per cent.); 30 associated croup, fatality 16.6 per cent. (corrected 6.6 per cent.).

It will be observed that in the last two reports the excess in

fatality in the "associated" diphtherias is much less striking than in Roux's statistics, and in some cases disappears altogether. This I am inclined to attribute to failure of the methods employed to indicate properly the division into pure and mixed infections, for the testimony is unanimous that the serum is of far less benefit in mixed diphtheria than in uncomplicated diphtheria, the most common and dangerous complicating micro-organism being the streptococcus pyogenes.

Most noteworthy has been the improvement in the results of serum therapy of diphtheria in the Paris hospitals since Roux's original communication to the Congress in Buda-Pest in September, 1894. The fatality has descended from Roux's original percentage of 26, in the later reports, to 14.7, 12, and 10 per cent., and, according to a recent statement of Moizard and Bouchard (July, 1895), it at present oscillates between 8 and 14 per cent. These are the best results which have hitherto been reported from any hospital for any large number of cases, and they are certainly most significant. As Moizard and Bouchard in their recent communication say, "This result can no longer be attributed to fortunate series of cases, as was claimed at the beginning by adversaries of the method. Thousands of patients have been treated, and it can now be said that the controversy is closed." This striking descent from Roux's first figures is not, however, attributed by the writers wholly to improvements in the methods of serum-therapy. As Roux pointed out in his first paper, the hygienic conditions in the two Paris hospitals from which these statistics come were very bad. These conditions have since then been greatly improved, and this reform has been especially manifest in the reduction of the deaths from broncho-pneumonia.

A most important classification of diphtheria for estimating the curative value of antitoxic serum is that into cases without and with laryngeal stenosis, and especially when such degrees of stenosis are considered as require operative interference by tracheotomy or intubation. I have therefore prepared the following table (Table II.), which gives the results of antitoxin treatment in operated and not operated cases of diphtheria. This, of course, is not equivalent to a division into anginas and croup, as many cases of croup are included in the non-operated cases; but I have desired to submit

the new method of treatment to the most severe test. No one can claim that laryngeal diphtheria requiring intubation or tracheotomy is anything but a severe disease. If the benefits of antitoxin are unmistakably manifested in these operated cases of croup, then the test is an *experimentum crucis*, and puts an end to the objections of those who assert that the apparently favorable results of serum-therapy in diphtheria are attributable mainly to the large proportion of mild cases treated.

The same reports with a few additional ones, for which references are given, have been used for Table II. as for Table I., but many of the reports in Table I. were not available for this table, as the writers did not always present their results in a form which fitted into the classification adopted. The table gives for each report the total number and fatality of cases treated, as in Table I., the number and fatality of cases not operated on (including cases of croup), the number and fatality of cases operated on, "T" signifying tracheotomy, "I" intubation, "I and T" signifying intubation followed by tracheotomy, and, so far as reported, the previous or simultaneous percentages of fatality from operation in cases treated without antitoxin. In the final column are pertinent statements concerning the cases in the series. Some reports are inserted which do not give the number of cases under the different headings. These, of course, cannot be used in the summary giving the totals.

Table II.—Fatality in Operated and Not-operated Cases of Diphtheria Treated with Antitoxin.

T, signifies tracheotomy; I, intubation; I and T, intubation followed by tracheotomy.

Reporter.	Total cases.	Deaths.	Not operated cases.	Deaths.	Operated cases.	Deaths.	Previous fatality from operation.	Remarks.
Roux, Martin, and Chaillou,	300	78 (26 p. ct.)	179	22 (12.8 p.ct.)	121 T	56 (46 p. ct.)	67 p. ct.	Deducting those which died in less than 24 hours after admission to the hospital, there remain 107 tracheotomies with 42 deaths (39.2 per cent.)
Kossel,	117	13 (11.1 p.ct.)	94	1 (1.1 p.ct.)	23 T	12 (52.2 p. ct.)	....	In all of the fatal operations it was necessary to perform tracheotomy within 12 hours after admission.
Körte,	121	40 (33.1 p.ct.)	79	18 (22.8 p.ct.)	42 T	22 (52.4 p. ct.)	77.5 p. ct.	Of 8 tracheotomized cases under 2 years of age, 5 died (62.5 per cent.). The previous fatality for tracheotomy under 2 years was 90.7 per cent.).
Sonnenburg,	95	16 (16.8 p.ct.)	61	8 (13.1 p.ct)	34 T	8 (23.5 p. ct.)	38 p. ct.	The fatality of 38 per cent. in the table is that of 47 tracheotomies performed during the period in which the supply of antitoxin temporarily was exhausted and could not at once be replaced.
Baginsky,	525	83 (15.6 p.ct.)	430	47 (10.9 p ct.)	95 { 53 T / 54 I (in 12 cases tracheotomy followed intubation.)	36 { 34 T / 2 I } 37.8 p.c. (of the secondary tracheotomies 12 died (37.9 per ct.)	64.4 p. ct. T 44.8 p. ct. I	During two months in which the supply of serum failed the general fatality rose to 48.4 per cent., and that from tracheotomy and intubation to 62.2 per cent. The fatality at once fell upon reintroduction of the antitoxin treatment.
v. Widerhofer,	300	71 (23.7 p.ct.)	192	20 (10.4 p.ct)	108 T or I	51 (47.2 p. ct.)	.....	22 cases of laryngeal diphtheria (croup) recovered without operation.
v. Ranke,	96	19 (19.7 p.ct.)	54	6 (11.1 p.ct.)	42 I	13 (30.9 p. ct.)	61-75 p. ct.	21 cases of croup recovered without operation.
Stintzing,	59	12 (20.1 p.ct.)	43	5 (11.6 p.ct.)	16 T	7 (44 p. ct.)	49 p. ct.	
Schröder,	63	8 (12.7 p.ct)	32	5 (15.6 p.ct.)	31 T	3 (9.67 p. ct.)		
Vierordt,	63	16 (25 p. ct.)	48	9 (18.75 p.ct.)	15 T	7 (46 p. ct.)	.....	Deducting 8 cases in a hopeless condition on admission, there was only one death among the non-tracheotomized cases, a death-rate of only 2.7 per cent.
Rumpf,	22	2 (8 p. ct.)	15	0	7 T	2 (28.6 p. ct.)		
Lebreton and Magdelaine,	258	31 (12 p. ct.)	183	8 (4.4 p.ct.)	75 { 24 T / 51 I	23 { 9 T (37.5 p.c.) / 14 I (27.5 p.c.)	73.2 p. ct. T	Of the intubated cases 7 died in less than 24 hours after admission. Deducting these, the fatality from intubation was only 18.1 per ct.

Reporter.	Total cases.	Deaths.	Not-operated cases.	Deaths.	Operated cases.	Deaths	Previous fatality from operation.	Remarks.
Le Gendre, Moizard and Perregaux. Sevestre and Meslay,	398	52 (13.1 p.ct.)	316	23 (7.6 p.ct.)	82 { 51 T; 21 I; 10 I & T	29 { 20 T (39.2 p.c.); 5 I (23.8 p.c.); 4 I&T (40 p.c.) (35.4 per ct.)	86 p. ct. T	Deducting 15 deaths in less than 24 hours after admission, the total fatality is reduced to 9.7 per cent. These cases are those treated in the Hôpital Trousseau, in Paris, from the middle of September to December 25, 1894.
Ganghofner,	110	14 (12.7 p.ct.)	66	8 (12 p.ct.)	44 I or T	6 (13.6 p. ct.)	59.8–78 p. ct.	12 laryngeal diphtherias recovered without operation. During period in which the supply of serum failed the general fatality rose to 53.2 per cent., and that of operated cases to 68.9 per cent.
Soltman,	89	13 (14.6 p.ct.)	48	2 (4.2 p.ct.)	41 I	11 (27 p. ct.)	68 p. ct.	
Bokai,	120	31 (25.5 p.ct.)	71	10 (14 p.ct.)	49 I	21 (43 p. ct.)	70 p. ct.	In 14 cases presenting symptoms of moderate laryngeal stenosis upon admission these symptoms disappeared after injection of antitoxin without operation.
Heim,	27	6 (22 p.ct.)	21	4 (19 p.ct.)	6 { 2 T; 4 I	2 { 1 T (50 p. ct.); 1 I (25 p. ct.) 33.3 per ct.	.....	During period when supply of serum failed, the general fatality rose to 65.6 per et. Heim treated altogether 48 cases in two groups, but of his second group of 21 cases, 12 were still under treatment at date of report, and these are not included in my table.,
Börger,	30	2 (6.66 p.ct.)	25	1 (4 p ct.)	5 T	1 (20 p ct.)	.....	313 cases of diphtheria treated in the same hospital (Greifswald) from Oct. 1893, to Sept. 1894, gave a fatality of only 14.5 per cent.
Moeller,	76	27 (35.5 p.ct.)	28	8 (28.6 p.ct.)	48 T	19 (39.6 p. ct.)	55.6 p. ct.	
Kuntzen,	25	3 (12 p. ct.)	20	1 (5 p.ct.)	5 T	2 (40 p. ct.)		
Charon,	13	4 (30 8 p.ct.)	2	0	11 T	4 (36.4 p. ct.)		
Washbourn, Goodall, and Card,	72	14 (19.4 p.ct.)	63	11 (17.5 p.ct.	9 T	3 (33.3 p. ct.)	91.7 p. ct.	In 13 previous series of 9 tracheotomies in each group the average of deaths numbered 8¼.
Herringham,	18	3 (16.7 p.ct.)	7	0	11 { 10 T; 1 I	3 (30 p. ct.) T	65 p. ct. T	The 7 unoperated cases were mild.
Germonig, (Civic Hosp. of Trieste.)	224	42 (18.7 p.ct.)	178	18 (10 p.ct)	46 { 2 T; 44 I	24 I (54.5 p. ct.)	85.5 p. ct. T 75 p. ct. I	During a period of exhaustion of the supply of serum the general fatality rose to 50 per et. These data are from abstracts in the British Med. Journ., Feb. 2, 1895, and the Deutsche med. Wochenschrift, 1894, No. 52. The general serum fatality is variously given as 18.7, 20.3, and 22 per cent.
Witthauer,	36	5 (14 p. ct.)	16	1 (6.25 p.ct.)	20 T	4 (20 p. ct.)	25 p. ct.	Only one adult in this series.
Rapmund,	100	7 (7 p. ct.)	98	7 (7.1 p.ct)	2 T	0	.....	Collection of cases treated in private practice by several physicians in Minden.
Heidenhain,	24	3 (12.5 p.ct.)	22	2 (9.1 p.ct.)	2 T	1 (50 p. ct.)		
Risel,	114	9 (7.9 p.ct.)	95	5 (5.3 p.ct.)	19 T	4 (21 p. ct.)		

v. Muralt,	58	2 (3.4 p.ct.)	38	0	20 { 14 I; 2 T; 4 I & T }	2 (10 p. ct.)	....	After intubation (14 cases) no deaths; after intubation and tracheotomy one death; after tracheotomy one death.
D'Espine,	60	6 (10 p. ct.)	49	2 (8.2 p.ct.)	11 T	4 (36.4 p. ct.)	.....	10 cases of croup recovered without operation.
v. Engel,	39	10 (25.5 p.ct.)	30	7 (23.3 p.ct.)	9 T	3 (33.3 p. ct.)	85 p. ct.	The fatality of 42 unoperated cases not treated with antitoxin was 33.4 per cent., that of 20 tracheotomized cases not so treated 85 per ct.
Codd and Whitehouse,	11	4 (36.4 p.ct.)	7	2 (28.6 p.ct.)	4 { 3 T; 1 I }	0 I 2 T (66.6 p. ct.) 50 p. ct. of operated cases.	.....	Three of the four deaths were from croup.
Winkfield,	22	4 (18.2 p.ct.)	19	2 (10.5 p.ct.)	3 T	2 (6.66 p. ct.)	85.7 p. ct.	
Sigel,	100	12 (12 p.ct.)	No. of cases not given	.....	No. of cases not given.	(20.3 p. ct.) T.	63.3–70 p. ct.	The fatality of tracheotomized cases in 1894, up to the date of beginning treatment (Oct. 4) was 70 per cent.; after treatment with antitoxin 20.3 per cent.
Galatti,	No. of cases not given	....	No. of cases not given	.....	15 I	6 (40 p. ct.)	52.6 p. ct. I	Quoted in Le Bulletin Médical, 1895, p. 364.
Kraske,	Not given	.....	.....	.....	16 T	5 (31.25 p. ct.)	28 p. ct. (in 12 cases)	Says that he has tracheotomized 12 cases not treated with antitoxin with a fatality of only 38 per cent. Abst. in Münchener med. Wochenschrift, 1894, p. 1062.
Bonain,	Not given	.....	.....	.....	5 I	2 (40 p. ct)	60.5 p. ct.	Le Bulletin Médical, April 17, 1895.
Van Nes,	52	12 (23 p.ct.)	30	4 (13.3 p.ct.)	22 { 15 T; 7 I }	8 (36 p. ct.) I & T	48–73 p. ct.	During ten preceding years the lowest fatality of operated cases was 52 per ct., not operated 16 per ct. In three groups of 52 cases each, preceding the introduction of antitoxin treatment, the lowest fatality of operated cases was 48 per ct., of not operated cases 19 per ct.
Leichtenstern & Wendelstadt	123	25 (20.3 p ct.)	86	9 (10.4 p.ct.)	37 T	16 (43.2 p. ct.)	64 p. ct.	Of 17 tracheotomized cases less than 2 years old, 9 died; between 2 and 4 years, 4 out of 11 died, of 13 unoperated cases under 2 years, 2 died; of 21 between 2 and 4 years, 2 died.
Kohts,	39	Not given	Not given	(9.1 p.ct.)	Not given.	30.77 p. ct. T	.....	Abst Münchener med. Wochenschrift, June 11, 1895.
Timmer,	31	6 (19.4 p.ct.)	25	5 (20 p ct.)	6 T or I	1 (16.6 p. ct.)		
Mason,	306	81 (26.4 p.ct)	275	62 (22.5 p.ct.)	31	19 (61 p. ct.)	90 p. ct. ?	The statement is that the fatality from tracheotomy was reduced by the antitoxin about one-third.
Kurth,	97	10 (10.3 p.ct.)	82	7 (8.5 p.ct.)	15 T	3 (20 p. ct.)	.....	Of 32 cases of laryngeal diphtheria not operated upon, 30 recovered.
Total of 38 reports,	4294	784 (18.3 p.ct.)	3127	350 (11.2 p.ct.)	1167	434 (37.2 p. ct.)	.....	Of the total cases 27.2 per cent. were operated upon by tracheotomy or intubation.

In 41 reports there are 648 tracheotomies with 258 deaths, a fatality of 39.8 per cent.; 342 intubations with 99 deaths, a fatality of 28.9 per cent., and 26 intubations followed by tracheotomy with 14 deaths, a fatality of 53.8 per cent.

There are 211 operated cases in which it is not stated how many are tracheotomy or intubation. These gave a fatality of 40.2 per cent. They were probably for the most part tracheotomies.

The reports giving the previous or simultaneous fatality from tracheotomy contain 510 cases of tracheotomy, with 217 deaths, or 42.5 per cent. If the fatality of these cases be reckoned on the basis of the preceding or simultaneous fatality, selecting the lowest figures given, there would have been 329 deaths, or 64.5 per cent. There was, therefore, an apparent reduction in fatality of 34.1 per cent. by the serum treatment.

Making a similar estimate on the basis of previous fatality from intubation, there were 250 intubations, with 79 deaths, or 31.6 per cent., instead of 156 deaths, or 62.4 per cent. There was, therefore, an apparent reduction in the fatality of intubated cases of 49.5 per cent., as the result of serum treatment.

The fatality of 3127 non-operated cases was only 11.4 per cent.

Of the 4294 cases in Table II., 27.2 per cent. required tracheotomy or intubation. There were, however, many more cases of laryngeal diphtheria in this group than the ratio of operative cases would indicate, for it is the testimony of the great majority of the observers that the stenotic symptoms of laryngo-tracheal diphtheria are relieved without the necessity of operation in a much larger proportion of the cases treated with antitoxin than by any other method of treatment. As is well known, recovery without intubation or tracheotomy from descending laryngo-tracheal diphtheria, especially in children, is exceptional under all other methods of treatment, and the greater relative frequency with which such recovery occurs under serum treatment is a strong proof of the efficacy of antitoxin.

Of Kossel's 44 cases of laryngeal diphtheria treated with antitoxin, 21 (47.7 per cent.) recovered without operation; of von Widerhofer's 130 stenotic cases treated with serum, 22 (16.9 per cent.) recovered without operation; of von Ranke's 63 cases, 21

(33.3 per cent.); of Vierordt's 24 cases, 9 (37.5 per cent.); of Ganghofner's 56 cases, 12 (21.4 per cent.); of Bokai's 63 cases, 14 (22.2 per cent.); of d'Espine's 21 cases, 10 (47.6 per cent.). Von Ranke says that before the use of serum at most 5 per cent. of his cases of laryngeal stenosis escaped operation, whereas now 33 per cent. escape. Of Ganghofner's stenotic cases formerly 12 per cent. escaped operation, whereas now 21 per cent. escape. The experience of Heubner and many others is similar.

In this respect, as in so many others, the results in the Paris hospitals have been most favorable. Of Moizard and Perregaux's 145 cases of croup, 90 (62.1 per cent.) recovered without intubation or tracheotomy. Roux, Martin, and Chaillou say:

"Of 169 children, admitted to the service for diphtheric angina, 56 presented laryngeal symptoms; 31 had hoarse voice, and in 25 the voice was so far extinguished and the dyspnœa (tirage) so marked that one might believe that the latter patients should be operated on. Under the influence of the serum (and in these cases one should not fear to make an injection every twelve hours) the dyspnœa diminished, then occurred only paroxysmally, the child coughed up false membrane, and at the end of two or three days the respiration became normal to the great astonishment of the interns and personnel of the pavilion who, with their large experience of children affected with croup, indeed, thought that operation could not be avoided. To-day, in the presence of a child with dyspnœa, it is not necessary to press for operation. One can inject the serum and wait as long as possible. Since the introduction of the serum the number of tracheotomies in the pavilion has diminished."

Out of his large experience Baginsky expresses himself in these vigorous words:

"Here, again, the observation of the individual cases of laryngeal stenosis, and more especially of those which do not come to the point of operation, speak to me more forcibly than the statistical figures. The surprising regression of the laryngo-stenotic respiratory phenomena, the freedom of breathing, the disappearance of the hoarse voice and the croupy cough, the euphoria of the children, the change in their general condition, so that two days after the injection they are sitting up in bed, playing and contented and observant of their surroundings; all of these things produce in him who has had before his eyes for years the hopeless picture of continually progressing laryngeal stenosis, in very truth, ineffaceable impressions."

Experience based upon such a large number of cases and careful clinical observation must be regarded as representing the norm.

That there may be deviations from this norm, even in a fair number of cases, seems to be illustrated by the experience of Leichtenstern and Wendelstadt, who in 123 cases of diphtheria with 37 tracheotomies, were not able to note any material reduction in the proportion of cases requiring tracheotomy as compared with former series of cases. Their observations were uncontrolled by bacteriological diagnoses.

Another point to be considered in this connection is of capital importance as an indication of the value of serum treatment. Cases which are free from symptoms of laryngeal involvement at the time of injection of the serum do not develop such symptoms later, or do so only very exceptionally, unless evidences of such involvement appear within twenty-four hours after the injection.

Regarding neither this nor any other point is there entire unanimity of opinion in the various reports, nor is such to be expected from observers of limited numbers of cases with unequal distribution in the various groups of mild cases, of early cases, of anginas, of croup, of pure diphtheria, of septic diphtheria, etc., to say nothing of the absence in some reports of any bacteriological control of the diagnosis and of treatment by insufficient doses or inferior quality of serum. I am only surprised that the conflicting statements are not more numerous. But there are not many points concerning which there are so few differences of statement as concerning the efficacy of antitoxin in preventing descent of the diphtheritic process to the larynx and the trachea. Over and again one can read in the reports such statements as that in all of the patients who entered without laryngeal diphtheria the larynx remained free, or that unless the symptoms of stenosis appeared within the first twenty-four hours after injection of the serum they were not observed at all, or only most exceptionally. Among the many vouchers for these statements may be cited Kossel, Roux, Baginsky, von Widerhofer, Heubner, von Ranke, Vierordt, Ganghofner, Escherich, Bokai, Van Nes, Kurth.

It is this power of antitoxin to check the spread of the diphtheritic process from the tonsils and pharynx into the larynx, and from the larynx into the bronchi, which has impressed many observers in favor of the new treatment more forcibly than any other feature of their experience with its action. Thus Vierordt

observed that of 24 children with diphtheria who were admitted with unaffected larynx, and treated with antitoxin, only one developed temporarily a hoarse cough on the third day. In all of the others the larynx remained free. Of 23 patients who were admitted with unaffected larynx not long before the introduction of the serum treatment, nine afterward developed croup. This is doubtless a somewhat unusual experience as regards the large proportion of cases of croup developing under previous methods of treatment.

It follows from what has been said that the ratio of operative cases in antitoxin statistics will in general be smaller than in statistics of cases of the same character treated by other methods. On the one hand there will be fewer laryngeal stenoses developing after commencement of the treatment, and on the other hand a larger number of recoveries from laryngeal diphtheria without the necessity of operation.

The following figures serve to illustrate this point. In the service from which the cases reported by Roux were derived tracheotomy was performed before the serum period in 50 per cent. of the cases of diphtheria, after the introduction of serum in 40 per cent. The later Paris reports give a much greater reduction in the ratio of tracheotomies. In Baginsky's service 43.9 per cent. of the cases were operated on before the use of serum, and 18.1 per cent. after its introduction; in von Ranke's service the corresponding figures are 57 per cent. before and 43.5 per cent. after; in Bokai's, 65.6 per cent. before and 40.8 per cent. after. As already mentioned, Leichtenstern's figures, 32 per cent. before and 30 per cent. after serum, are exceptional.

It is furthermore to be considered that in view of the power of antitoxin to abate beginning and moderate symptoms of stenosis, operation will be delayed rather than hastened, and, when performed, the indications for it will generally be urgent. For manifest reasons, most of the operations will fall within a period not remote from the time of injection of the serum. Of the 121 tracheotomies in the report of Roux, Martin, and Chaillou, 102 were performed either before the first injection of antitoxin, or within twelve hours afterward; 14 between the twelfth and the thirty-sixth hour after inception of the serum treatment, and only 5 later than thirty-six hours after the injection of the serum. Of the 23 tracheotomies

with 12 deaths reported by Kossel the operation was performed within the first twelve hours in all of the fatal cases, and of the 11 successful cases it was performed in 9 on the day of admission to the hospital, in 1 on the second day, and in 1 on the following day. Kossel refers the increase in the stenotic symptoms after injection of the serum in the last two cases to the separation of the false membranes, a point to which others have also called attention as an effect of antitoxin, and which is to be borne in mind in cases of croup treated by antitoxin.

Turning now to the results of tracheotomy and intubation in cases treated with antitoxin, we find in Table II. that in 41 reports there were 648 tracheotomies with 258 deaths, a fatality of 39.8 per cent., and 342 intubations with 99 deaths, a fatality of 28.9 per cent , and 26 intubations followed by tracheotomy, with 14 deaths, a fatality of 53.8 per cent. These are not unheard-of fatalities from these operations, but they are so low as to indicate decidedly remedial action of antitoxin.

The percentage of fatality from tracheotomy in diphtheria given by Monti from a total of 12,736 cases up to 1887 is 73.3. The percentage given by V. Hirsch in 1654 tracheotomies in diphtheria in von Bergman's clinic in Berlin during the last ten years and seven months (up to July 31, 1894), is 68.7 per cent., the fatality during the first four years of this period being 70.5 per cent., and during the last four years 63.8 per cent. The fatality during the first year of life was 98.8 per cent., and sank for each year to the ninth, when it was 41.7 per cent., and after the tenth year it rose again.

More proper, however, than comparison with these latter percentages is comparison with the percentages of fatality in the same hospital or place from which the respective groups of cases are reported. It will be observed that with one exception in the table the percentage of deaths following operation in cases treated by antitoxin is lower, and generally very much lower, than the previous or simultaneous fatality. Kraske's exceptional series is of so few cases (only 5 with and 12 without serum) as to be without any significance. The lowest fatality thus far reported in a series is 3 deaths in 31 tracheotomies with serum treatment, or a fatality of only 9.67 per cent. This is reported by Schroeder from the hospital in Altona.

If for each group of cases we estimate the number of deaths which would have occurred in the tracheotomized cases treated with serum, on the assumption that the previous or simultaneous fatality in cases not treated with serum had obtained, we obtain the following result: The actual percentage of deaths in 510 tracheotomized cases treated with serum was 42.5. The percentage of fatality in these cases, estimated on the basis of previous or simultaneous fatality in the same hospitals, would be 64.5. There was, therefore, an apparent reduction in fatality by the serum treatment of 34.1 per cent. This difference between actual and estimated fatality is greater than is observed in any ordinary experience of variations in fatality during a series of years in the same hospital from tracheotomy in diphtheria.

I confess to some surprise that the analysis of the tracheotomized cases treated by serum should have yielded results so strikingly favorable to antitoxin treatment. When one considers that the benefits of serum treatment are most strikingly apparent when the treatment is begun early in the disease, and become more and more doubtful after the third day, it would not have been a convincing argument against the treatment if these benefits were not conspicuously manifest in cases of diphtheria requiring tracheotomy, for, as has been explained, the great majority of these tracheotomized cases are already the subject of advanced laryngeal stenosis when the antitoxin is first injected. There are, however, not a few cases which begin apparently as laryngeal diphtheria (croup d'emblée), or in which the involvement of the larynx occurs within twenty-four or forty-eight hours after the onset of the attack. That careful observation would reveal in many of these apparently primary or early laryngeal diphtherias a latent or slightly manifested diphtheric angina, I believe to be true.

It is interesting to note that in several reports the benefit of serum treatment has been much more evident in the operated cases than in those not operated on, although this is not the rule. Indeed, Leichtenstern and Wendelstadt find in their series of 123 cases that the difference in favor of the serum in their non-operated cases was so small as to be without significance, whereas there was a difference in favor of the serum of 20.8 per cent. in their tracheotomized cases, with and without serum treatment. They attribute,

therefore, the entire benefit of the serum, in their experience, to its action in tracheotomized cases. Their experience, however, is exceptional, although in a measure approached by that of Ganghofner and of Van Nes. On the other hand, in Vierordt's experience the entire benefit of antitoxin seemed to be in the non-operated cases. As has been repeatedly explained, such diversities of experience with limited numbers of cases are to be expected, and the norm can be established only by observations of large numbers of cases in different places and at different times. This norm is that both operated and not-operated cases are benefited by antitoxin, and that the difference in each class between serum fatality and fatality from other methods of treatment is a large one.

The fatality of intubated cases in Table II. treated with antitoxin is 28.9 per cent., which is 10.9 per cent. less than the fatality of tracheotomized cases. Before the introduction of the serum treatment a collective investigation was set on foot by the German Gesellschaft für Kinderheilkunde to determine the average fatality following intubation. In 1893 von Ranke reported to the Society that 1445 cases of diphtheria with laryngeal stenosis treated by intubation gave a mortality of 62.5 per cent. This result was interpreted in favor of intubation as opposed to tracheotomy. There is a difference of 33.6 per cent. between this percentage and that obtained from our 342 intubated cases treated with antitoxin. This difference is so great that, after making all due allowance for possible differences in the series of cases entering into the two groups of statistics, it seems impossible to explain it otherwise than as a powerful additional support of the arguments already presented in support of the claims of antitoxin. Here, certainly, the objection that the cases treated by antitoxin were light ones cannot be made.

Table II. enables us to compare the fatality of 250 intubated cases treated with antitoxin with the fatality estimated on the assumption that the previous or simultaneous fatality from intubation in the same hospital had obtained in the several groups. By this calculation we find the actual fatality to be 31.6 per cent., and the estimated fatality 62.4 per cent. In other words, there was an apparent reduction in the fatality of intubated cases of 49.5 per cent., as the result of the serum treatment.

However distrustful one may be of statistical evidence in thera-

peutics—and previous experience justifies much distrust—I fail to see on what credible assumption this striking reduction of fatality can be explained otherwise than as demonstrative of the specific curative power of antitoxin in diphtheria.

Lamentable for the victims, but adapted to convince the skeptical, were the experiences of Baginsky and of Ganghofner during the periods of failure in the supply of serum. During the enforced two months' interruption of the serum treatment (August and September) in Baginsky's service there were 116 cases of laryngostenosis with a fatality of 62.2 per cent., as opposed to a fatality of 37.8 per cent. in the serum periods which preceded and followed the pause. The percentage of operations rose to 55.2, as opposed to 18.1 per cent. during the periods of serum treatment, and this without any change in the general character of the cases admitted. During the serum periods there were more intubations than tracheotomies, whereas during the pause there were 45 tracheotomies and 19 intubations, 13 of the latter requiring secondary tracheotomy. In Ganghofner's service the fatality of the operated cases rose from 13.6 per cent. to 68.9 per cent. during the interruption in the supply of serum.

There remain two points to be touched upon before dismissing the laryngeal stenoses. These are the substitution of intubation for tracheotomy in a larger and larger proportion of the laryngeal diphtherias requiring operative interference and treated by the serum, and the shortening of the period during which the tube or the tracheal canula is required to be kept in the air-passage.

An agent which would arrest the progressive descent of the diphtheritic process from the larynx into the bronchi and hasten the disappearance of the obstructive exudate is just what was needed to make intubation the ideal operation for the relief of the great majority of cases of croup requiring operative interference. Such an agent we now possess in antitoxin for a large group of cases, and we are not surprised, therefore, to find that the employment of intubation, as a substitute for tracheotomy, has been greatly extended by the introduction of serum therapy.

Several writers give figures showing that serum therapy materially hastens the time when extubation or removal of the tracheal canula is permissible, but I have not attempted to collect these figures.

Of the 3127 not-operated cases, including, as already stated, many cases of croup, 350 died, giving a fatality of 11.2 per cent. In V. Hirsch's statistics of diphtheria from von Bergmann's clinic for ten years the average fatality of not-operated cases (1004) was 26 per cent., varying only from 25.9 per cent. during the first four years of the period to 27.3 per cent. during the last four years. There is, however, no general standard of fatality for cases of diphtheria not operated on. The variations are within very wide limits, as might be expected. Only a comparatively small number of the reports give separately the previous or simultaneous fatality of non-operated cases not treated with serum. I find in the reports the following data on this point. In Roux, Martin, and Chaillou's report the previous fatality of non-operated cases averaged 33.9 per cent., the minimum being 32.1 per cent. and the maximum 47.3 per cent., as opposed to 12.8 per cent. under the serum treatment; in Baginsky's report the corresponding figures are 31.6 per cent. *versus* 10.9 per cent.; in Bokai's, 34.5 per cent. *versus* 14 per cent.; in Ganghofner's, 15.8 per cent. (the lowest in a series of years) *versus* 12 per cent.; in Van Nes's, 33 per cent., the average of ten years, with a minimum of 16 per cent. and a maximum of 41 per cent., *versus* 13.3 per cent.; in Leichtenstern and Wendelstadt's, 15 per cent. *versus* 10.4 per cent.

Age is a factor of such prime importance in the prognosis of diphtheria that I have prepared the following table (Table III.), in which the cases treated with serum, collected from twenty-five reports, are classified according to age. Unfortunately, there is very little uniformity of system in the different reports in giving the results according to the ages of the patients, many of the reports simply stating the number of adults or the maximum age of the children, or the number of cases under a certain age, or the number between arbitrarily selected limits of age, etc., so that many of the reports were not used for the following table. In each space in the table the upper number is the total number of the cases belonging to the heading, and the lower number is the number of deaths among these cases.

TABLE III.—AGES OF PATIENTS TREATED WITH ANTITOXIN.

In each space the upper number is that of the cases, and the lower that of the deaths.

Reporter.	Total cases.	Und. 1 yr.	1–2 years.	2–3 years.	3–4 years.	4–5 years.	5–6 years.	6–7 years.	7–8 years.	8–9 years.	9–10 years.	10–12 years.	12–15 years.	Over 15 yrs	Remarks.
Kossel,	117	3	4	18	14	20	10	11	10	7	7	12	1		
	13 (11 p. ct.)	1	0	2	3	3	2	0	0	1	0	0	1		
Körte,	121	...	...	...	...	...	...	...	...	...	...	...	..		Of 15 infants under 2 years, 8 recovered and 7 died.
	40 (33.1 p. ct.)														
		Under 2 yrs.		2–4 years.		4–6 years.		6–8 years.		8–10 years.					
Baginsky,	525	87		146		116		79		58		20	15	...	Of 4 cured cases the ages are not stated.
	83 (15.6 p. ct.)	22		25		20		9		3		2	2		
v. Widerhofer,	100	8	24	20	14	16	5	7	2	1	...	2	1	...	Deutsche med. Wochen., Jan. 10, 1895.
	24 (24 p. ct.)	5	9	7	6	3	0	0	0	0		0	0		
		Under 2 yrs.					2–10 years.					Over 10 years.			
Schröder,	63	6					52					5			
	8 (12.7 p. ct.)	3					4					1			
Bokai,	120	1	22	22	24	18	13	6	7	2	1	4	...		69 cases were under 3 years of age.
	31 (25.5 p. ct.)	1	10	7	4	3	1	1	3	0	0	1			
Heim,	27	...	5	4	2	6	3	2	2	...	...	3			
	6 (22 p. ct.)		1	1	0	2	0	0	2			0			
											8–13 years.				
Unterholzner.	31	2	9	7	3	2	1	2	2			3			Of 21 under 4 years of age, 13 recovered.
	8 (25.8 p. ct.)	1	5	2	0	0	0	0	0			0			
Börger,	30	...	...	1	2	1	1	3	2	2	2	3	2	11	16 cases were 10 years old or over.
	2 (6.6 p. ct.)			0	0	0	1	0	0	0	0	1	0	0	
											Over 6 years.				
Hager,	25	1	1	1	3	6	4				9				
	1 (4 p. ct.)	0	0	0	0	1	0				0				
Seiz,	27	1	4	2	6	4	4	1	2	3	...	...	...	...	Private practice.
	1 (3.6 p. ct.)	0	0	1	0	0	0	0	0	0					
		Under 4 years.				4–6 years.				7–15 years.					
Seitz,	35	18				10				7					One fatal case was 13 months, the other 18 months old; both with laryngeal diphtheria.
	2 (5.7 p. ct.)	2				0				0					
								5–10 years.				10–15 years.			
Reported in Brit. Med. Journ., Feb. 2, 1895,	95	4	9	6	12	10		23				15		16	
	22 (23.2 p. ct.)	2	3	1	1	3		9				2		1	

Reporter.	Total cases.	Und. 1 yr.	1–2 years.	2–3 years.	3–4 years.	4–5 years.	5–6 years.	6–7 years.	7–8 years.	8–9 years.	9–10 years.	10–12 years.	12–15 years.	Over 15 yrs.	Remarks.
Goodall,	72	4	10	7	9	10			22			10		...	Brit. Med. Journ., Jan. 12, 1895. These are the ages of cases previously reported by Washbourn, Goodall, and Card.
	14 (19.4 p. ct.)	1	2	1	3	5			2			0			
Hall,	11	...	1	...	...	...	...	1	...	1	...	1	2	5	
	3 (27.3 p. ct.)		0					1		1		0	1	0	
Epidemic in Trieste, hosp. cases.	105	9	12	12	15	16	13	7	6	4	2	6	...	3	
	27 (25.7 p. ct.)	5	5	6	3	5	1	0	1	0	1	0		0	
Epidemic in Trieste, private practice.	72	...	2	3	8	11	12	5	1	7	2	3	7	1	Ten cured cases are not accounted for in this series.
	5 (6.9 p. ct.)		0	2	1	1	0	0	0	1	0	0	0	0	
												10–13 years.			
Blumenfeld,	50	...	6	5	...	5	5	14	5		...	9		1	Private practice.
	2 (4 p. ct.)		1	0		0	0	0	1			0		0	
Schaewen,	15	...	1	...	...	1	2	...	3	...	3	2	2	1	Private practice.
	0		0			0	0		0		0	0	0	0	
					3–5 years.				5–10 years.			10–20 yrs.		Over 20	
Rapmund,	100	1	6	12	22				43			15		1	Private practice. 14 cases were under treatment at time of report.
	7 (7 p. ct.)	0	1	2	1				3			0		0	
			1–3 years.						Over 3 years.						
v. Muralt,	58	...		21					37						The latter fatal case was of a tracheotomized child, 4 years old, admitted on the sixth day of the disease; the former case was of an infant, 2 years old, with syphilis, measles, and pneumonia.
	2 (3.4 p. ct.)			1					1						
Codd and Whitehouse,	11	1	...	1	...	1	1	1	...	2	2	...	1	1	The fatal case was a woman, 39 years old, admitted in a state of collapse the 8th day of the disease, and dying in 24 hrs.
	4 (36.4 p. ct.)	0		1		1	0	0		0	0		1	1	
Winkfield,	22	...	1	2	...	4	2	3	2	3	...	2	1	2	
	4 (18.2 p. ct.)		1	1		0	1	1	0	0		0	0	0	
Van Nes,	52	..	1	7	4	9	8	7	6	3	2	5			
	12 (23 p. ct.)		0	4	2	4	0	0	1	1	0	0			
			0–2 years.		2–4 years.				Over 4 years.						
Leichtenstern & Wendelstadt	123		30		32				61						Of 17 tracheotomized infants less than 2 years old, 9 died.
	25 (20.3 p. ct.)		11		6				8						Of 13 unoperated patients less than 2 years old, 2 died.
															Of 11 tracheotomized patients between 2 and 4 years, 4 died.
															Of 21 unoperated cases between 2 and 4 years, 2 died.

As the cases in the preceding table were not classified according to the ages by a uniform plan in the different reports, they cannot all be summarized in a single table, but the chief results can be presented as follows:

14 reports.	Total.	0–2 years.	2–4 years.	4–6 years.	6–8 years.	8–10 years.	10–12 years.	12–15 years.	Over 15 yrs	Undetermined.
Cases	1234	187	327	297	176	114	63	32	24	(14)
Deaths	215	60	70	48	19	8	4	5	1	(0)
Percentages	17.4	32.1	21.4	16.2	10.8	7	0.63	1.6	4.1	(0)

In the following table the cases under four years are from twenty reports containing 1630 cases (fatality 17.6 per cent., and those over four years are from seventeen reports containing 1451 cases (fatality 17.4 per cent.).

	0–2 years.	2–4 years.	4–10 years.	10–15 years.	Over 15 yrs.
Cases	263	411	681	129	40
Deaths	86	84	95	11	2
Percentages	32.7	20.4	13.9	8.5	5

The following table gives the results for each year up to five and over five years.

18 reports.	Total.	Under 1 year.	1–2 years.	2–3 years.	3–4 years.	4–5 years.	Over 5 years.	Undetermined.
Cases	982	34	112	118	116	140	452	(10)
Deaths	179	16	37	36	17	31	42	(0)
Percentages	18.2	47.1	33	30.5	14.7	22.1	9.3	(0)

The table furthermore shows under one year 35 cases, with 16 deaths, or 45.7 per cent.; under two years 291 cases, with 97 deaths, or 33.3 per cent.; under three years 304 cases, with 93 deaths, or 30.6 per cent.; and under four years 692 cases, with 122 deaths, or 17.6 per cent. (each of these four groups of cases being from a total number of cases in the first group of 1082 cases, in the second group of 1914 cases, in third group of 1140 cases, and in the fourth group of 1665 cases, the average fatality for the whole number of cases being 17.3 per cent).

The most frequently quoted percentages of fatality in diphtheria, according to the age, are those of Herz, and are as follows :

Under 1 year	80 per cent.
1–3 years	45 "
3–5 "	40 "
5–10 "	17 "
Over 10 years	17 "

The percentages of fatality in V. Hirsch's statistics of 2658 cases from the surgical clinic in Berlin, for ten years and seven months (ending July 31, 1894), according to age, are :

Under 1 year	88.3 per cent.
1– 2 years	82.5 "
3– 4 "	63.9 "
4– 5 "	56.6 "
5– 6 "	46.9 "
6– 7 "	43.7 "
7– 8 "	36.1 "
8– 9 "	28.1 "
9–10 "	31.1 "
10–11 "	21.2 "
11–12 "	20.9 "
12–13 "	18.5 "
13–14 "	16.7 "
14–15 "	15 "
15–16 "	12.5 "
Adults (72 cases)	11.1 "

Baginsky gives the following percentages from his service in the Kaiser- und Kaiserin-Friedrich Children's Hospital, in Berlin, as the mean of the four years 1890 to 1893 inclusive :

Under 2 years	60.2 per cent.
2– 4 years	51.2 "
4– 6 "	38 "
6– 8 "	28.9 "
8–10 "	24.5 "
10–12 "	28.8 "
12–14 "	18.5 "

Baginsky's results in Table III. may be compared with this last list of percentages, otherwise I do not consider that these statistics of Herz, Hirsch, and Baginsky furnished any certain standard of

comparison for the percentages of fatality derived from Table III. I have cited them, however, in the absence of any such standard, to show in a general way that these latter percentages indicate a low fatality according to age. The contrast between a fatality percentage of 33.3 for cases of diphtheria under two years of age treated with serum, and that of 60 to over 80 for cases of the same age not so treated is a striking one, even if a large allowance be made for differences in the characters of the cases in the two groups.[1]

We come now to the consideration of the influence upon the fatality of the length of the interval between the onset of diphtheria and the first injection of antitoxin. In experiments upon animals this factor is decisive in determining the result. It is the factor which Behring from the first has put in the foreground. His claim is that no death will occur from diphtheria if antitoxin is injected in sufficient dose at the beginning of the disease, and that the fatality will fall under 5 per cent. if the treatment in proper manner is begun before the third day of the disease.

Of course, the only significance of this great emphasis upon the importance of early treatment is as an expression of the fact that cure is rendered more difficult the larger the number of the diphtheria bacilli, the greater the amount and intensity of their toxins, the greater the damage already inflicted by the bacilli and their toxins, and the more serious the complications and secondary infec-

[1] A second provisional report of the collective investigation instituted by the *Deutsche medicinische Wochenschrift*, has been published (August 8, 1895), but too late for consideration in the text of this article. Of 5833 cases of diphtheria treated with serum, tracheotomy was performed in only 5.4 per cent. of the cases. This material evidently is not well comparable with the great mass of statistics, chiefly from hospitals, already reported, but is probably representative of the experience in private practice. Of the cases treated with serum 12.6 per cent. were under two years of age; 69.1 per cent. were between two and ten years; and 18.3 per cent. were over ten years. Of the 4479 cases treated without serum, 11.1 per cent. were under two years; 60.5 per cent. were between two and ten years; and 28.4 per cent. were over ten years of age. The total fatality of the cases treated with serum was 9.6 per cent., that of cases treated without serum was 14.7 per cent. The significance of this difference in favor of serum is increased by the fact that 81.7 per cent. of the serum-treated cases were not over ten years of age, whereas only 71.6 per cent. of the cases treated without serum were not over ten years.

The fatality of the serum-treated cases under two years of age was 21.8 per cent. (11.8 per cent. when the treatment was begun on the first and second days of the disease), that of the cases treated without serum under two years was 39.7 per cent. The corresponding figures for ages between two and ten are for serum 8.8 per cent., and without serum 15.2 per cent.; over ten years of age, for serum, 4.1 per cent., without serum 3.7 per cent. These results would indicate that the benefits of the serum treatment are greatest in infants and are not apparent in adults. I think it is probable that the benefits of the treatment are most strikingly manifested in infants and young children, but other reports show that adults are also benefited.

A fuller report of these cases is promised.

tions. There is, however, no absolute parity between the length of time the disease has lasted before beginning treatment and the increase of these dangers. One case may become desperate within forty-eight hours after the onset, and another may present no grave symptoms after a week's duration. The virulence, the number, and the microbic associations of the infecting bacilli, and especially the local and general susceptibilities of the patient, are factors no less important than the single factor of time in influencing the issue.

The individual peculiarities of each case must be considered. If all is judged according to one simple uniform standard—antitoxin cures the case or it does not cure the case—and it must be confessed this is all which seems to be in the minds of many, then the practitioner will not come to any clear conception of the wonderful powers of the healing serum. The sins of some observers in this matter seem incredible. They lump together indiscriminately all of their cases, including those complicated with measles, scarlet fever, tuberculosis, and other diseases, the mixed infections, the anginas, the croups, the advanced and the early cases, the true and the false diphtherias, the infants and the adults, and throw them into the scale to be weighed for or against antitoxin. An unsuccessful case is put down to the discredit of antitoxin without reference to its peculiarities. On the basis of experience in treating a dozen cases the writer bodily attacks results established by the careful observation of hundreds of cases. It is true we need these brute figures for comparison with former fatality statistics of diphtheria, and they have served to demonstrate the curative efficacy of antitoxin; but reports of personal experience with the serum treatment should at least contain the data for an intelligent analysis of the cases treated. Such analysis is requisite in order to reveal the full scope and capabilities of the new treatment. We have already seen that the study of the cases with reference to laryngeal involvement has brought to light evidence in favor of the serum treatment more convincing than that derived from the gross statistics of all cases treated, and evidence of a kind which meets many of the objections which have been urged against the interpretation of the gross statistics as demonstrative of the efficacy of antitoxin. We shall now see that the analysis of the cases according to the day of the disease on which the serum treatment is begun almost, if not completely,

substantiates Behring's original claims, astounding as they seemed to be.

There is, of course, in many cases considerable uncertainty as to the exact duration of the disease at the time when the patient is first seen by the physician. The statements of parents, or of those in charge of the children, are often the only evidence on this point which can be obtained. Satisfactory information will be particularly difficult to obtain in the class of patients in the diphtheria wards of hospitals, these patients being chiefly the children of laborers. We are also to consider that a diphtheric affection of the throat may exist without such manifest disturbance as to attract even intelligent observation, or it may be mistaken for a simple sore-throat. A tabulation of cases of diphtheria according to the day of beginning treatment will be, therefore, only of relative value; but we may fairly assume that the duration of the disease will very rarely, if ever, be shorter, but often longer than that stated.

In the excellent reports on antitoxin treatment from the Paris hospitals the cases are not analyzed according to the day of beginning treatment, as Roux, whose scheme of classification has been followed by most other French writers, stated in his original article that it was practically impossible to obtain trustworthy statements on this point from parents of the children. Most of the reports, therefore, which enter into Table IV., are from German and English sources.

The statements as to the day of the disease are entirely from information obtained from parents and others, and are not estimates on the part of the physician, although in several instances the reporter says that the condition of the patient plainly indicated a longer duration of the disease than that assigned by the parents and put down in the report. It will be observed that not all of the reports in the table fit into any one system of classification, and, therefore, not all can be summarized in a single table. In each space the higher number is the total number of cases belonging to the heading, and the lower is the corresponding number of deaths.

TABLE IV.—FATALITY ACCORDING TO THE DAY OF DISEASE UPON WHICH ANTITOXIN IS INJECTED.

In each space the higher number is the total number of cases treated on the corresponding day, and the lower number is that of the deaths.

Reporter.	Total No. of cases.	1st day.	2d day.	3d day.	4th day.	5th day.	6th day.	After 6th day.	Undetermined.	Remarks.
Kossel,	117	14	30	29	9	11	6	12	6	Fatality for first three days was 1.4 per cent.
	13 (11.1 p. ct.)	0	1	0	1	2	3	5	1	
Körte,	121	...	...	...	...	...	...	...	...	Of 37 severe and moderately severe cases injected during the first three days of the disease, 8 died (21.6 p.ct.). The results following injection begun after the third day were less favorable.
	40 (33.1 p. ct.)									
Baginsky,	525	111	134	92	52	39	13	29	55	All of the three fatal cases of the first day were far advanced on admission, therefore the statements of the parents as to the date of beginning of the disease were probably erroneous (Baginsky). Mortality for first three days was 8.9 per cent.
	83 (15.6 p. ct.)	3	14	13	12	14	4	12	11	
v. Mering,	74	..	...	...	...	...	...	...	...	Treatment begun on the 1st or 2d day in nearly all cases.
	4 (5 p. ct.)									
v. Noorden,	81	...	...	...	...	...	...	...	...	Treatment begun on the 3d or later day in nearly all cases.
	19 (23 p. ct.)									
Schröder,	63		23		27		13			
	8 (12.7 p. ct.)		1		3		4			
Vierordt,	55	3	14	17	9	7	1	4		
	8 (14.6 p. ct.)	0	2	2	0	3	0	1		
Rumpf,	26	...	18	3	5		...	...	...	Four cases were still under treatment at date of report.
	2 (8 p. ct.)		1	1	0					
Ganghofner,	110	3	30	35	18	9	2	13		
	14 (12.7 p. ct.)	0	2	3	4	3	0	2		
Heim,	27	...	9	2	7	3	1	5		
	6 (22 p. ct.)		0	1	1	1	0	3		
Börger,	30	3	13	9	...	3	1	1		
	2 (6.6 p. ct.)	0	0	0		1	0	1		
Hager,	25	14	5	4	1	...	...	1	...	Private practice. The single fatal case died of complications after cessation of the diphtheria.
	1 (4 p. ct.)	1	0	0	0			0		
Kuntzen,	25	3	6	7	2	2	1	4		
	3 (12 p. ct.)	0	0	1	0	0	1	1		
Schmidt,	14	...	...	...	...	...	...	...	...	The three fatal cases were not treated until after the disease had existed for 8 to 14 days. Private practice.
	3 (21.4 p. ct.)									
Seitz,	35	...	10	12	9		4	...	...	The two deaths were infants 1½ years and 13 months old, with advanced laryngeal diphtheria on day of admission, presumably, therefore, treated after 2d or 3d day, although this is not stated.
	2 (5.7 p. ct.)									
Hall,	11	2	4	4	...	1	...	...	...	A girl, 10 years old, whose brother and sister had recently died of diphtheria, developed diphtheria while under observation in the hospital. Antitoxin was at once injected, and the next day membrane was smaller, temp. normal, and recovery promptly followed.
	3 (27.3 p. ct.)	0	0	2		1				
Epidemic in Trieste, hosp. cases,	105	6	30	29	20	11	7	2		
	27 (25.7 p. ct.)	0	5	9	5	4	3	1		

Reporter.	Total No. of cases.	1st day.	2d day.	3d day.	4th day.	5th day.	6th day.	After 6th day.	Undetermined.	Remarks.
Epidemic in Trieste, priv. pract.	72	14	27	18	8	2	2	1		
	5 (6.9 p ct.)	0	2	1	2	0	0	0		
Witthauer,	36	4	8	4	6	3	...	11		
	5 (14 p. ct.)	0	2	1	0	0		2		
Blumenfeld,	50	40		8		2	...	...	...	Of the two fatal cases, in one the treatment began on the 4th and in the other on the 5th day. Private practice.
	2 (4 p. ct.)	0		1		1				
Rapmund.	100	39	34	15	5	3	1	3	...	The deaths are given for the 1st and 2d, the 3d and 4th and the 5th, 6th and after 6th day respectively.
	7 (7 p. ct.)	2		3		2				
Schaewen,	15	6	3	...	..	1	...	...	5	Of the 5 undetermined cases the statement is that they had been ill several days before the injection.
	0	0	0			0			0	
Risel,	114	...	78	21	4	4	5	...	2	Eighty-nine of these cases were treated at their homes, and 25 in hospitals. They were mostly children.
	9 (7.9 p. ct.)		4	4	0	0	1		0	
v. Muralt,	58	11	18	17	After 3d day.		12			
	2 (3.4 p. ct.)	0	0	0			2			
Codd and Whitehouse.	11	1	2	5	...	2	...	1		
	4 (36.4 p. ct.)	0	0	2		1		1		
Winkfield,	22	...	8	7	4	2	...	1	...	Of the 2 fatal cases in which it is stated the injection was made on the second day, in one there were on admission advanced laryngeal and nasal diphtheria with glandular swellings, and in the other thick membranes in the throat, nasal discharge, and glandular swellings.
	4 (18.2 p. ct.)		2	1	1	0		0		
Howard,	40	24	7	2	2	3	2	...	...	Private practice.
	3 (7.5 p. ct.)	0	0	0	1	0	2			
Van Nes,	52	2	13	10	7	8	...	12	...	No details given of fatal case said to be treated on first day of the disease, but it is noted that the determination of the day was very uncertain in the class of patients (children of laborers) admitted.
	12 (23 p. ct.)	1	1	1	2	3		4		
Kurth,	97	12	35	16	19	5	3	7	...	Of the 2 fatal cases in which it is stated the injection began on the 2d day, one was admitted with croup, and died 18 hours afterward; the other died a month after disappearance of the local diphtheria with albuminuria and broncho-pneumonia.
	10 (10.3 p. ct.)	0	2	1	3	1	1	2		

The following table is the summary of the 19 reports of the preceding table, in which the number of the cases, with the results corresponding to the day of the disease on which antitoxin treatment was begun, is given for each day up to and after the sixth day :

19 reports.	Total.	1st day.	2d day.	3d day.	4th day.	5th day.	6th day.	After 6th day.	Undetermined.
Cases	1489	222	456	311	168	116	44	104	(68)
Deaths	212	5	37	42	32	34	15	35	(12)
Percentages	14.2	2.2	8.1	13.5	19	29.3	34.1	33.7	(17.6)

Including with the preceding 19 reports those of Schröder, Blumenfeld, and Rapmund, we have the following table, which gives the results of antitoxin treatment begun on the first and second, on the third and fourth, and after the fourth day.

22 reports.	Total.	1st and 2d day.	3d and 4th day.	After 4th day.	Undetermined.
Cases	1702	814	534	286	(68)
Deaths	229	45	81	91	(12)
Percentages	13.5	5.5	15.2	31.8	(17.6

It may also be computed from the table that of 1729 cases of diphtheria with a fatality of 14.9 per cent., 1115 cases treated with antitoxin during the first three days of the disease yielded a fatality of 8.5 per cent., whereas 546 cases in which antitoxin was first injected after the third day of the disease yielded a fatality of 27.8 per cent. Of 232 cases in which treatment was begun on the first day, 5 (2.15 per cent.) died; of 492 cases in which treatment was begun on the second day, 38 (7.7 per cent.) died; of 331 cases in which treatment was begun on the third day, 43 (13 per cent.) died.

As is well known, the fatality from diphtheria by any approved method of treatment is smaller the earlier in the disease the treatment is begun. This is clearly shown in the following table from the statistics of V. Hirsch of the cases treated in the surgical clinic in Berlin for ten years preceding August, 1894, and, of course, before the employment of antitoxin. The results are according to the day of the disease on which treatment was begun.

	1st day.	2d day.	3d day.	4th day.	5th day.	6th day.	7th and 8th day.	After 8th day.
Cases	241	405	323	416	203	525	506	239
Deaths	44	92	124	223	136	219	367	191
Percentages	18.3	22.7	38.1	53.6	67	67.4	72.5	81.6

The preceding table is not intended to serve as a standard of comparison for my tables giving the results of cases treated by antitoxin, as the classes of cases in the two groups are not comparable.

Philip[1] has reported from Baginsky's service the results of treatment before the use of antitoxin, begun in the earlier stages of diphtheria, the patients being brothers and sisters of children with diphtheria, who were examined for Loeffler bacilli, so that opportunity was given for recognition of the disease at its onset. The fatality was 10.5 per cent. lower in those cases recognized and treated early than in the others. The fatality of the cases treated by Baginsky with serum during the first three days of the disease was 32.2 per cent. lower than the preceding average fatality of cases not treated with serum. Plainly some more potent healing factor than merely that of early treatment was present. The only difference in the methods of treatment of the two groups of cases was the use of antitoxin in the one and its absence in the other.

Kohts, an opponent of the serum treatment, at the recent Congress for Internal Medicine in Munich, claims for his method of local treatment no deaths among cases treated on the first day of the disease. For later days his results are much higher than those in the serum statistics. The percentages of deaths, according to the day of beginning his treatment, as given by Kohts, without a statement of the number of cases treated, are as follows: first day, 0; second day, 20 per cent.; third day, 47 per cent.; fourth day, 55 per cent.

Table IV. shows that out of 232 cases in which it is alleged that antitoxin was injected on the first day of the disease, 5 died. As a matter of fact, however, the assumed duration of the disease in each of these fatal cases is doubtful, as it rests solely on the statements of parents or those who care for the children, and is apparently contradicted in at least the three cases, concerning which any details are given, by the condition of the patient on admission. Baginsky's three cases (Nos. 311, 479, and 511 of his table) when admitted were far advanced in the disease, with extensive membranous exudate, cyanosis, and very bad general condition. Hager's case may more readily be accepted, as it occurred in private prac-

[1] Philip: Arch. f. Kinderheilk., Bd. XVI.

tice; but here the patient died after disappearance of the diphtheria, from complications, whether or not referable to the diphtheria is not stated. Of the fifth fatal case reported by Van Nes no details are given in such form that the case can be identified from his description; but he himself places little reliance upon the alleged duration of the disease in the class of patients admitted to the hospital, these being the children of laborers.

I am not aware of the report of any fatal case of diphtheria properly treated by antitoxin within the first twenty-four hours after the beginning of the disease in which the duration was positively determined. A case reported by Ritter may be such, but the observation of Kurth, already cited, illustrates the difficulty of precise determination of the date of onset of diphtheria. There are, however, many such cases of prompt recovery reported as that quoted from Hall in Table IV.

It is noteworthy that the percentage of deaths in 814 cases, in which treatment was begun before the third day of the disease, is only 5.5. If we make allowance for the fact that the assigned duration of the disease can scarcely be shorter, but may readily be longer than the actual duration, then our tabulation of 1702 cases of diphtheria, according to the day of beginning treatment, nearly verifies Behring's original prediction. I do not, however, consider that it is justifiable from so small a number of cases and from material of the kind composing our table, to draw any definite conclusions as to the exact percentages of deaths according to the date of beginning treatment.

According to the table, the percentage of deaths in cases in which the serum treatment is begun on the third and fourth days of the disease is nearly three times greater than that in cases treated on the first and second days, and the percentage after the third day is three and one-fourth times greater than that of cases treated within the first three days.

We are, of course, not to infer from these results that antitoxin may not be beneficial when administered after the third and fourth days of the disease. There are cases which are still mild after this duration, but which subsequently become serious, and even in desperate cases antitoxin holds out some hope of cure.

It is apparent that the largest proportion of cures by antitoxin are

to be expected from private practice among those who call the physician in at an early stage of the disease. While a similar statement may be made concerning any other suitable method of treatment, it is not, I believe, true in the same measure as for the serum treatment.

The main purpose of this article has been the study of the evidence thus far published concerning the curative power of antitoxin in diphtheria. I do not propose to consider the practical points relating to the employment of antitoxin, nor to consider in detail the specific effects of injection of the healing serum. There has been much diversity of opinion as to these effects, and I shall present briefly the principal points which seem to me to be established.

Most writers approve of the continuance of such measures of local and general treatment as have hitherto been found to be useful, but recommend the avoidance of all irritating and caustic local applications.

The injection of the serum may be followed in a few hours by local pain, swelling, and redness, but there is no danger of abscess-formation if the serum is uncontaminated and proper antiseptic precautions are taken. In over 3000 injections Martin observed the formation of an abscess only three times.

In twenty-four to forty-eight hours after the injection the general condition is remarkably improved in the great majority of those patients who are in a condition to be benefited at all by antitoxin. This general improvement is accompanied by a fall of temperature, which may be a critical fall, especially if the disease is not far advanced; often it is a fall by lysis. Some hold that there may be a temporary rise of temperature as an immediate effect of the injection. Accompanying the fall of temperature is improvement of the pulse as to frequency and tension, but the heart's action may for some time, even into the period of convalescence, remain weak.

In the favorable cases the local diphtheritic process is arrested, usually within the first twenty-four hours after the injection. Membrane may appear upon spots previously inflamed and invaded by the bacilli, but otherwise there is no extension of the membrane in the majority of the cases which are benefited. The area covered by membrane becomes sharply demarcated, and the swelling of adjacent

mucous membrane disappears. The membrane may disappear by rapid separation or by gradual softening. Sometimes it persists for several days after disappearance of all other local disturbance. Large membranous casts are coughed up from the larynx, trachea, and bronchi under the serum treatment more frequently than under former methods. The rapid separation of the membrane in the lower air-passages may cause sudden increase of stenotic symptoms. Nasal discharge is lessened.

The swelling of the glands in the neck and the surrounding œdema disappear, so far as these are not referable to secondary infections.

The most uncertainty prevails as to the influence of antitoxin in preventing the three most important complications or sequelæ of diphtheria : nephritis, heart-failure, and paralysis. The weight of evidence is that genuine nephritis is far less common in cases treated by antitoxin sufficiently early than under other methods of treatment; but it is questionable whether albuminuria is less common, although it is considered to be by Kossel, Roux, and others. If there is an albuminuria in any way directly referable to the injection of the serum, and this is by no means established, it is simple albuminuria, with, perhaps, a few narrow hyaline casts, but without evidence of any serious damage to the kidney. Peptonuria, it is claimed by Hecker, is an effect of the serum, but it is without clinical significance. Albuminuria is such an extremely common symptom of diphtheria that it must be very difficult to determine that it can be referred to the serum in any case.

Many writers emphasize especially the favorable influence of antitoxin upon the heart, but there are some who have observed that with decided improvement in all other symptoms the force of the heart may still remain weak and occasion anxiety. Baginsky's experience is that the minor disturbances of the cardiac action are not less frequent in cases treated with serum—they appear to be even more frequent, as a larger number of cases survive—but that actual death from heart-failure is far less common in the serum cases than in others.

Post-diphtheric paralyses may occur in cases treated with serum as early as the second or third day of the disease. Whether they occur in cases treated within the first twenty-four hours is not cer-

tain. Probably they do not. According to some, paralysis is even more common in the serum cases than under former methods of treatment. This is doubtful; but if true, it may be attributed to the survival of a larger proportion of cases.

It is apparent from what has been said that antitoxin is most strikingly beneficial in progressive fibrinous diphtheria, and especially in the prevention and cure of laryngeal diphtheria. In septic diphtheria the serum treatment is of little avail.

Antitoxic serum may produce unpleasant effects, but these do not involve danger to the patient. They are in all probability referable to the serum as such and not to the healing, so-called antitoxic, substance contained in the serum. The most common undesired effect is some form of exanthem, usually erythema and urticaria, sometimes an eruption like measles or scarlatinal rash. The same exanthems have been observed by Bertin after the injection of ordinary serum of the horse, and by Richardière after injection of Marmorek's anti-streptococcus serum. The serum from some horses is more likely to cause these exanthems than that from others, and there may be individual idiosyncrasies favoring their occurrence. Some writers report the occurrence of an exanthem in not more than 5 per cent. of their cases, others have observed them in over 50 per cent. of the cases treated with serum. They may be localized in the neighborhood of the seat of injection or extend from that over the greater part of the body, or make their first appearance at a distance from the point of injection. Often, without noticeable fever, they may be accompanied by considerable elevation of temperature and by pain and swelling in the joints A rarer but more severe form of serum exanthem resembles erythema multiforme, and when this is accompanied, as it may be, by high fever and severe pain in the bones and joints, with swelling of the joints, the condition of the patient may really seem serious. But these patients recover. Some have attributed a petechial eruption to injection of the serum, but this may occur in diphtheria without serum treatment.

These occasional untoward effects of the healing serum are annoying, but, being unattended with danger to life and without serious consequences, they do not contraindicate the use of the serum.

There have been a few cases reported in which the writers, without any satisfactory evidence whatever, have referred the death of

the patient to the use of the serum. The essential harmlessness of the serum has been demonstrated by over a hundred thousand injections,[1] and if future investigations should show that through some idiosyncrasy on the part of the patient death ever is attributable to the injection of the serum, this would probably count for about as much as the rare deaths from the use of ether or chloroform. I shall leave untouched the question of the immunizing properties of antitoxin.

The principal conclusion which I would draw from this paper is that our study of the results of the treatment of over seven thousand cases of diphtheria by antitoxin demonstrate beyond all reasonable doubt that anti-diphtheric serum is a specific curative agent for diphtheria, surpassing in its efficacy all other known methods of treatment for this disease. It is the duty of the physician to use it.

The later reports show in general a decided improvement in the results of the treatment over the earlier ones, and there is every reason to believe that the results of the second year's employment of the new treatment will make a much more favorable showing than those of the first year. We shall come to a clearer understanding of the mode of action of the healing serum. Improvements in the methods of preparation and preservation of the serum, and possibly the separation of the healing substance, at least from other ingredients which produce the undesired effects, may be expected.

The discovery of the healing serum is entirely the result of laboratory work. It is an outcome of the studies of immunity. In no sense was the discovery an accidental one. Every step leading to it can be traced, and every step was taken with a definite purpose and to solve a definite problem.

These studies and the resulting discoveries mark an epoch in the history of medicine. It should be forcibly brought home to those whose philozoic sentiments outweigh sentiments of true philanthropy that these discoveries, which have led to the saving of untold thousands of human lives, have been gained by the sacrifice of the lives of thousands of animals, and by no possibility could have been made without experimentation upon animals.

[1] This would seem to be at least a moderate estimate, as, writing November 20, 1894, Behring says that there had been up to that date certainly over 40,000 injections (Das neue Diphtheriemittel, von Dr. Behring, Berlin, 1894, p. 25).